Patent
Docket No. 57070US002

# Amido Ether Substituted Imidazoquinolines

This application claims the benefit of previously filed Provisional Application Serial No. 60/254,218, filed on December 8, 2000.

## Field of the Invention

This invention relates to imidazoquinoline compounds that have ether and amido functionality at the 1-position, and to pharmaceutical compositions containing such compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals, and in the treatment of diseases, including viral and neoplastic diseases.

## Background of the Invention

The first reliable report on the 1*H*-imidazo[4,5-*c*]quinoline ring system, Backman et al., J. Org. Chem. 15, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, Jain et al., J. Med. Chem. 11, pp. 87-92 (1968), synthesized the compound 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., Chem. Abs. 85, 94362 (1976), have reported several 2-oxoimidazo[4,5-*c*]quinolines, and Berenyi et al., J. Heterocyclic Chem. 18, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-c]quinolines.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. These are described in, *inter alia*, U.S. Patent Nos. 4,689,338; 4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640, all of which are incorporated herein by reference.

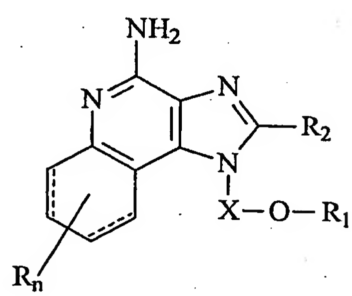
There continues to be interest in the imidazoquinoline ring system.

Certain 1H-imidazo[4,5-c] naphthyridine-4-amines, 1H-imidazo [4,5-c] pyridin-4-amines, and 1H-imidazo[4,5-c] quinolin-4-amines having an ether containing substituent at the 1 position are known. These are described in U.S. Patent Nos. 5,268,376; 5,389,640; 5,494,916; and WO 99/29693.

Despite these attempts to identify compounds that are useful as immune response modifiers, there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

## Summary of the Invention

We have found a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Accordingly, this invention provides imidazo[4, 50c]quinoline-4-amine and tetrahydroimidazo[4, 5-c]quinoline-4-amine compounds that have an ether containing substituent at the 1-position. The compounds are defined by Formulas (I) and(II), which are defined in more detail *infra*. These compounds share the general structural formula:



wherein X, $R_1$, $R_2$, and R are as defined herein for each class of compounds having Formulas (I) and (II).

The compounds of Formulas (I) and (II) are useful as immune response modifiers due to their ability to induce cytokine biosynthesis and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

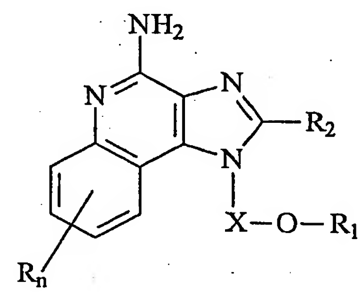
The invention further provides pharmaceutical compositions containing the immune response modifying compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral infection in an animal, and/or treating a neoplastic disease in an animal by administering a compound of Formula (I) or (II) to the animal.

In addition, the invention provides methods of synthesizing the compounds of the invention and novel intermediates useful in the synthesis of these compounds.

## Detailed Description of the Invention

As mentioned earlier, we have found certain compounds that induce cytokine biosynthesis and modify the immune response in animals. Such compounds are represented by Formulas (I) and (II) as shown below.

Imidazoquinoline compounds of the invention, which have ether and amide functionality at the 1-position, are represented by Formula (I):



(I)

wherein: **X** is $-CHR_5-$, $-CHR_5$-alkyl-, or $-CHR_5$-alkenyl-;

**$R_1$** is selected from the group consisting of:

$-R_4-CR_3-Z-R_6-$alkyl;

$-R_4-CR_3-Z-R_6-$alkenyl;

$-R_4-CR_3-Z-R_6-$aryl;

$-R_4-CR_3-Z-R_6-$heteroaryl;

$-R_4-CR_3-Z-R_6-$heterocyclyl;

$-R_4-CR_3-Z-H$;

$-R_4-NR_7-CR_3-R_6-$alkyl;

$-R_4-NR_7-CR_3-R_6-$alkenyl;

each $\mathbf{R_5}$ is independently H or $C_{1-10}$ alkyl;

$\mathbf{R_6}$ is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

$\mathbf{R_7}$ is H, $C_{1-10}$ alkyl, or arylalkyl; or $R_4$ and $R_7$ can join together to form a ring;

$\mathbf{R_8}$ is H or $C_{1-10}$ alkyl; or $R_7$ and $R_8$ can join together to form a ring;

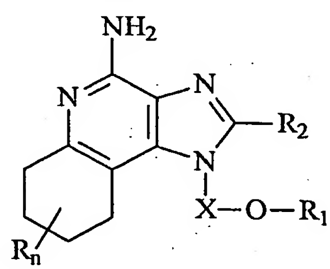
each **Y** is independently –O– or $-S(O)_{0-2}-$;

**n** is 0 to 4; and

each **R** present is independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{1-10}$ alkoxy, hydroxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

The invention also includes tetrahydroimidazoquinoline compounds that bear an ether and amide containing substituent at the 1-position. Such tetrahydroimidazoquinoline compounds are represented by Formula (II):



(II)

wherein: **X** is $-CHR_5-$, $-CHR_5$-alkyl-, or $-CHR_5$-alkenyl-;

$\mathbf{R_1}$ is selected from the group consisting of:

$-R_4-CR_3-Z-R_6-$alkyl;

$-R_4-CR_3-Z-R_6-$alkenyl;

$-R_4-CR_3-Z-R_6-$aryl;

$-R_4-CR_3-Z-R_6-$heteroaryl;

$-R_4-CR_3-Z-R_6-$heterocyclyl;

$-R_4-CR_3-Z-H$;

$-R_4-NR_7-CR_3-R_6-$alkyl;

-$R_4$–$NR_7$ –$CR_3$–$R_6$—alkenyl;

-$R_4$–$NR_7$–$CR_3$–$R_6$–aryl;

-$R_4$–$NR_7$–$CR_3$–$R_6$–heteroaryl;

-$R_4$–$NR_7$–$CR_3$–$R_6$–heterocyclyl;

-$R_4$–$NR_7$ –$CR_3$–$R_8$;

each **Z** is independently –$NR_5$–, –O–, or –S–;

**$R_2$** is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-CO-$N(R_5)_2$;

-CO-$C_{1-10}$ alkyl;

-CO-O-$C_{1-10}$ alkyl;

-$N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each **$R_3$** is =O or =S;

each $\mathbf{R_4}$ is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each $\mathbf{R_5}$ is independently H or $C_{1-10}$ alkyl;

$\mathbf{R_6}$ is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

$\mathbf{R_7}$ is H, $C_{1-10}$ alkyl, or arylalkyl; or $R_4$ and $R_7$ can join together to form a ring;

$\mathbf{R_8}$ is H or $C_{1-10}$ alkyl; or $R_7$ and $R_8$ can join together to form a ring;

each **Y** is independently –O– or $-S(O)_{0-2}-$;

**n** is 0 to 4; and

each **R** present is independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{1-10}$ alkoxy, hydroxy, halogen, and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R, $R_2$, $R_3$, $R_4$, X, Z and n are as defined above and $R_{11}$ is -$R_6$-alkyl, -$R_6$-aryl, -$R_6$-heteroaryl or -$R_6$-heterocyclyl where $R_6$ is as defined above.

In step (1) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula X is alkylated with a halide of Formula XI to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XII. The alcohol of Formula X is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form an alkoxide. Alternatively, the alkoxide can be formed by adding the alcohol to a biphasic mixture of aqueous 50% sodium hydroxide and an inert solvent such as dichloromethane in the presence of a phase transfer catalyst such as benzyltrimethylammonium chloride. The alkoxide is then combined with the halide. The reaction can be carried out at ambient temperature. Many compounds of Formula X are known, see for example, Gerster, U.S. Patent 4,689,338; others can readily be prepared using known synthetic routes, see for example, Gerster et al., U.S. Patent No. 5,605,899 and Gerster, U.S. Patent No. 5,175,296. Many halides of Formula XI are commercially available; others can be readily prepared using known synthetic routes.

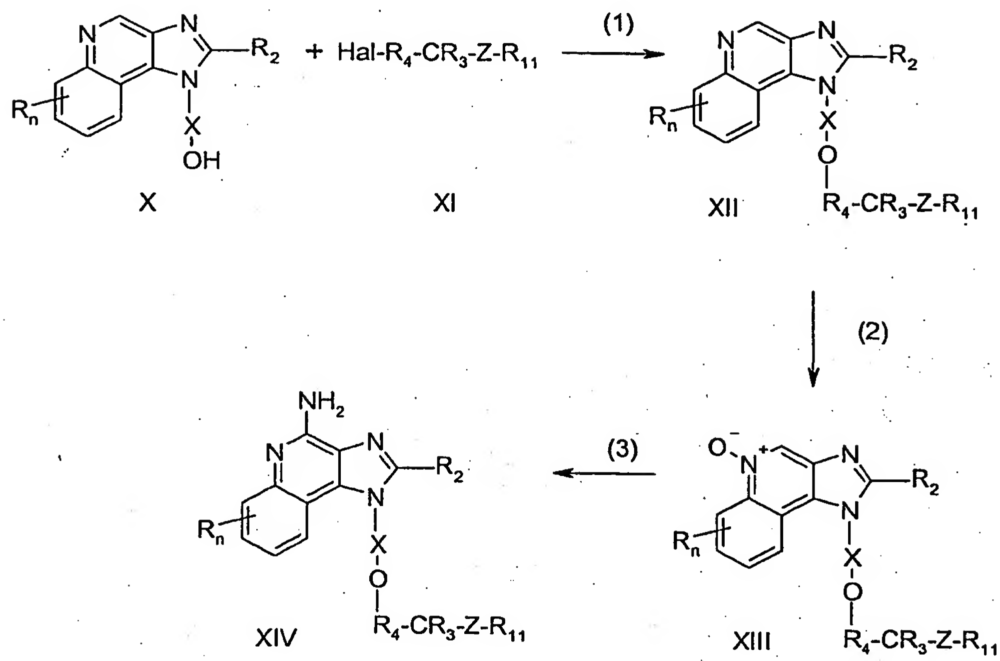
In step (2) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula XIII using a conventional oxidizing agent capable of forming N-oxides. Preferably a solution of a compound of Formula XII in chloroform is oxidized using 3-chloroperoxybenzoic acid at ambient temperature.

In step (3) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula XIII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV which is a subgenus of Formula I. Step (3) involves (i) reacting a compound of Formula XIII with an acylating agent and then (ii) reacting the product with an aminating agent. Part (i) of step (3) involves reacting an N-oxide of Formula XIII with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benezenesulfonyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride). Arylsulfonyl chlorides are preferred. *Para*-toluenesulfonyl chloride is most preferred. Part (ii) of step (3) involves reacting the product of part (i) with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g., in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). Ammonium hydroxide is preferred. The reaction is preferably carried out by dissolving the N-oxide of Formula XIII in an inert solvent such as dichloromethane, adding the aminating agent to the solution, and then slowly adding the acylating agent. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (3) may be carried out by (i) reacting an N-oxide of Formula XIII with an isocyanate and then (ii) hydrolyzing the resulting product. Part (i) involves reacting the N-oxide with an isocyanate wherein the isocyanato group is bonded to a carbonyl group. Preferred isocyanates include trichloroacetyl isocyanate and aroyl isocyanates such as benzoyl isocyanate. The reaction of the isocyanate with the N-oxide is carried out under substantially anhydrous conditions by adding the isocyanate to a solution of the N-oxide in an inert solvent such as chloroform or dichloromethane. Part (ii) involves hydrolysis of the product from part (i). The hydrolysis can be carried out by conventional methods such as heating in the presence of water or a lower alkanol optionally in the presence of a catalyst such as an alkali metal hydroxide or lower

alkoxide. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R, $R_2$, $R_4$, $R_7$, $R_{11}$, X and n are as defined above and BOC is *tert*-butoxycarbonyl.

In step (1) of Reaction Scheme II the amino group of an aminoalcohol of Formula XV is protected with a *tert*-butoxycarbonyl group. A solution of the aminoalcohol in tetrahydrofuran is treated with di-*tert*-butyl dicarbonate in the presence of a base such as sodium hydroxide. Many aminoalcohols of Formula XV are commercially available; others can be prepared using known synthetic methods.

In step (2) of Reaction Scheme II a protected aminoalcohol of Formula XVI is converted to an iodide of Formula XVII. Iodine is added to a solution of triphenylphosphine and imidazole in dichloromethane; then a solution of a protected aminoalcohol of Formula XVI in dichloromethane is added. The reaction is carried out at ambient temperature.

In step (3) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula X is alkylated with an iodide of Formula XVII to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XVIII. The alcohol of Formula X is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form an alkoxide. The iodide is added to the alkoxide solution at ambient temperature. After the addition is complete the reaction is stirred at an elevated temperature (~100°C).

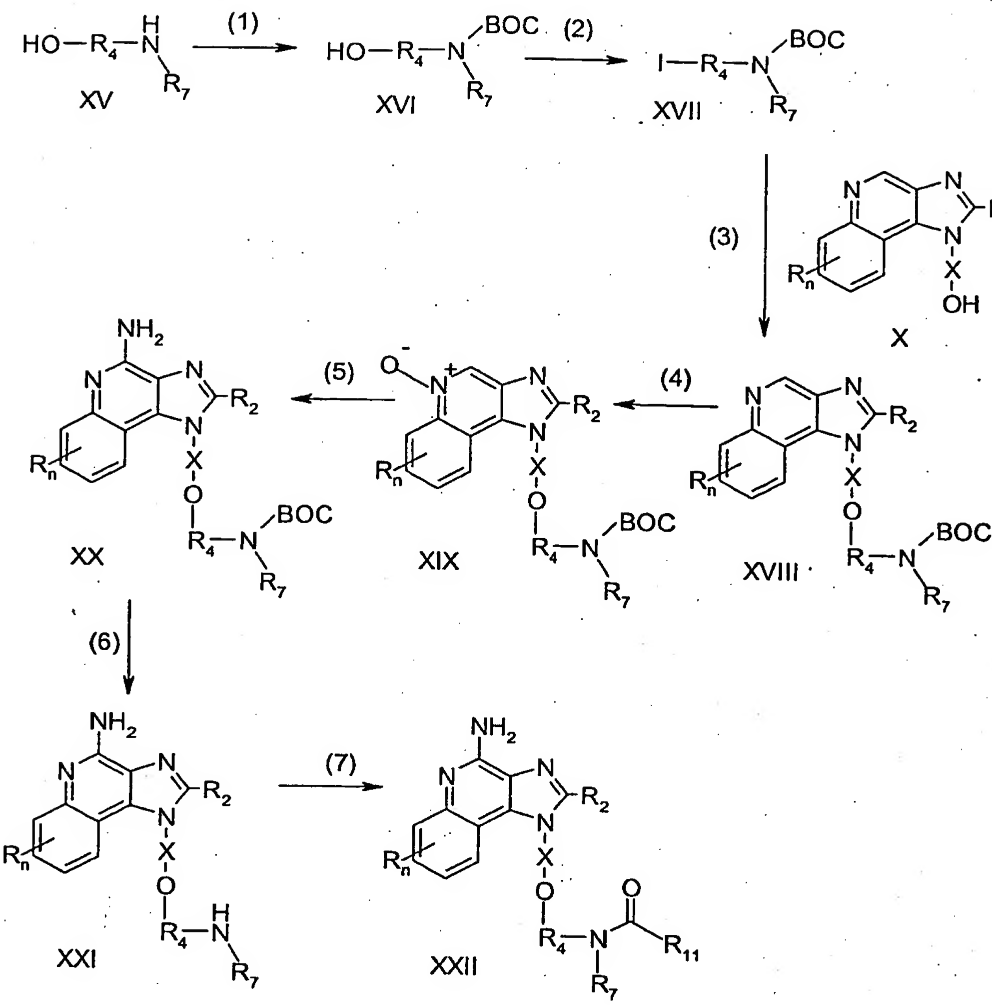
In step (4) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XVIII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula XIX using a conventional oxidizing agent capable of forming N-oxides. Preferably a solution of a compound of Formula XVIII in chloroform is oxidized using 3-chloroperoxybenzoic acid at ambient temperature.

In step (5) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinoline-5N-oxide of Formula XIX is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XX. Step (5) involves (i) reacting a compound of Formula XIX with an acylating agent and then (ii) reacting the product with an aminating agent. Part (i) of step (5) involves reacting an N-oxide of Formula XIX with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benezenesulfonyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride). Arylsulfonyl chlorides are preferred. *Para*-toluenesulfonyl chloride is most preferred. Part (ii) of step (5) involves reacting the product of part (i) with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g., in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). Ammonium hydroxide is preferred. The reaction is preferably carried out by dissolving the N-oxide of Formula XIX in an inert solvent such as dichloromethane or 1,2-dichloroethane with heating if necessary, adding the aminating agent to the solution, and then slowly adding the acylating agent. Optionally the reaction can be carried out in a sealed pressure vessel at an elevated temperature (85-100°).

In step (6) of Reaction Scheme II the protecting group is removed by hydrolysis under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXI. Preferably the compound of Formula XX is treated with hydrochloric acid/ethanol at ambient temperature or with gentle heating.

In step (7) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXI is converted to an amide of Formula XXII which is a subgenus of Formula I using conventional synthetic methods. For example, a compound of Formula XXI can be reacted with an acid chloride of Formula $R_{11}C(O)Cl$. The reaction can be carried out by adding a solution of the acid chloride in a suitable solvent such as dichloromethane or 1-methyl-2-pyrrolidinone to a solution of a compound of Formula XXI at ambient temperature. Alternatively, a compound of Formula XXI can be reacted with an acid of Formula $R_{11}COOH$. The reaction can be carried out at ambient temperature in a solvent such as dichloromethane or pyridine using a standard coupling reagent such as 1,3-dicyclohexylcarbodiimide or 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



Compounds of the invention can be prepared according to Reaction Scheme III where R, $R_2$, $R_4$, $R_7$, $R_{11}$, X and n are as defined above and BOC is *tert*-butoxycarbonyl.

In step (1) of Reaction Scheme III the amino group of an aminoalcohol of Formula XXIII is protected with a *tert*-butoxycarbonyl group. A solution of the aminoalcohol in tetrahydrofuran is treated with di-*tert*-butyl dicarbonate in the presence of a base such as sodium hydroxide. Many aminoalcohols of Formula XXIII are commercially available; others can be prepared using known synthetic methods.

In step (2) of Reaction Scheme III a protected amino alcohol of Formula XXIV is converted to a methanesulfonate of Formula XXV. A solution of a compound of Formula XXIV in a suitable solvent such as dichloromethane is treated with methanesulfonyl chloride in the presence of a base such as triethylamine. The reaction can be carried out at a reduced temperature (0°).

In step (3a) of Reaction Scheme III a methanesulfonate of Formula XXV is converted to an azide of Formula XXVI. Sodium azide is added to a solution of a compound of Formula XXV in a suitable solvent such as N,N-dimethylformamide. The reaction can be carried out at an elevated temperature (80 - 100°C).

In step (3b) of Reaction Scheme III a compound of Formula XXVI is alkylated with a halide of Formula Hal-$R_7$ to provide a compound of Formula XXVII. In compounds where $R_7$ is hydrogen this step is omitted. The compound of Formula XXVI is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form the anion and then combined with the halide. The reaction can be carried out at ambient temperature.

In step (4) of Reaction Scheme III an azide of Formula XXVI or XXVII is reduced to provide an amine of Formula XXVIII. Preferably, the reduction is carried out using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as methanol or isopropanol.

In step (5) of Reaction Scheme III a 4-chloro-3-nitroquinoline of Formula XXIX is reacted with an amine of Formula XXVIII to provide a 3-nitroquinoline of Formula XXX. The reaction can be carried out by adding an amine of Formula XXVIII to a solution of a compound of Formula XXIX in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. Many quinolines of Formula XXIX are known compounds or can be prepared using known synthetic methods, see for example, U.S. Patent 4,689,338 and references cited therein.

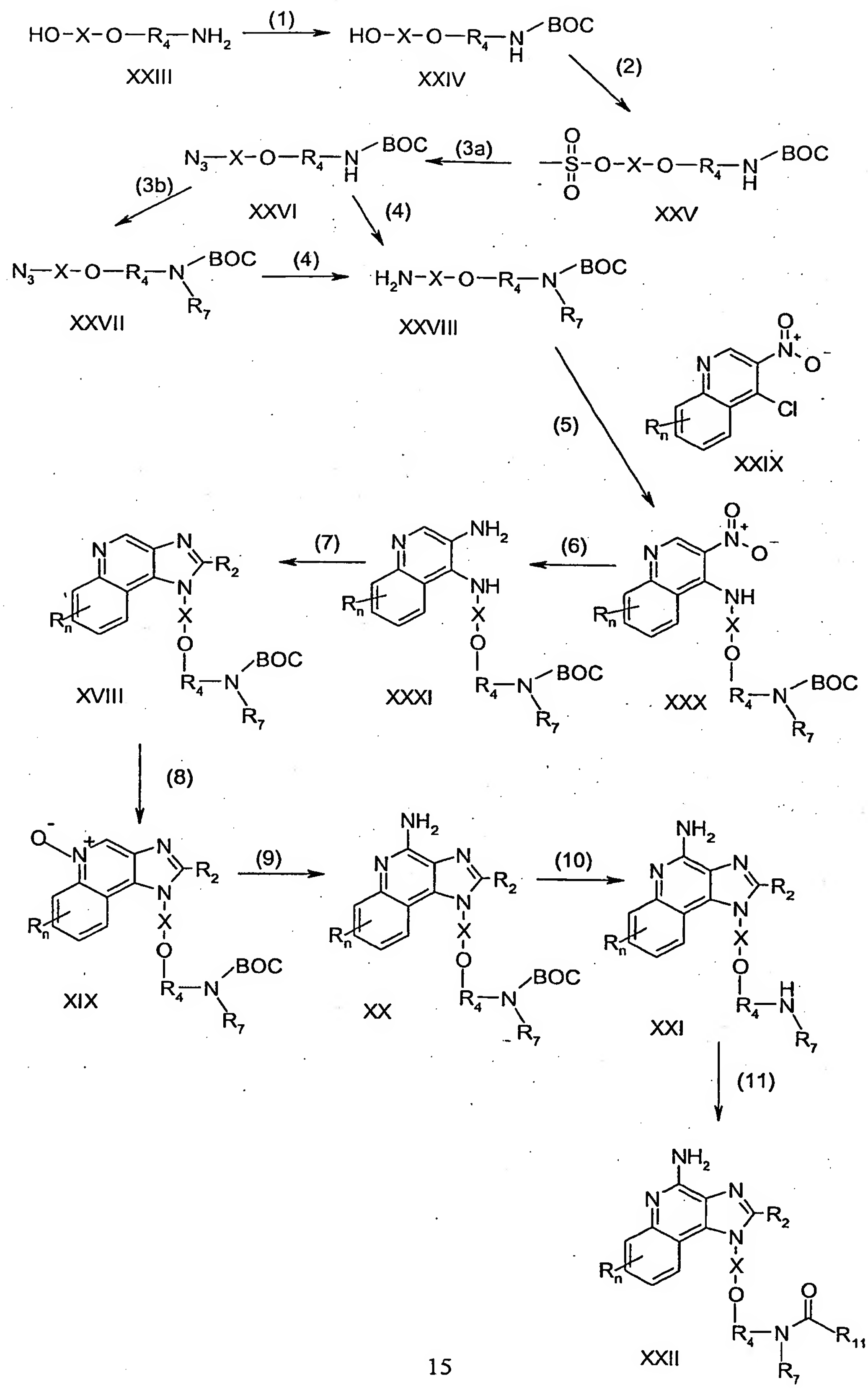
In step (6) of Reaction Scheme III a 3-nitroquinoline of Formula XXX is reduced to provide a 3-aminoquinoline of Formula XXXI. Preferably, the reduction is carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as toluene.

In step (7) of Reaction Scheme III a compound of Formula XXXI is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XVIII. Suitable equivalents to carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired $R_2$ substituent in a compound of Formula XVIII. For example, triethyl orthoformate will provide a compound where $R_2$ is hydrogen and triethyl orthovalerate will provide a compound where $R_2$ is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

Alternatively, step (7) can be carried out by (i) reacting a compound of Formula XXXI with an acyl halide of Formula $R_2C(O)Cl$ or $R_2C(O)Br$ and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula XXXI in an inert solvent such as acetonitrile or dichloromethane. The reaction can be carried out at ambient temperature or at a reduced temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. Preferably the product of part (i) is refluxed in ethanol in the presence of an excess of triethylamine or heated with methanolic ammonia.

Steps (8), (9), (10) and (11) are carried out in the same manner as steps (4), (5), (6) and (7) of Reaction Scheme II.

Reaction Scheme III



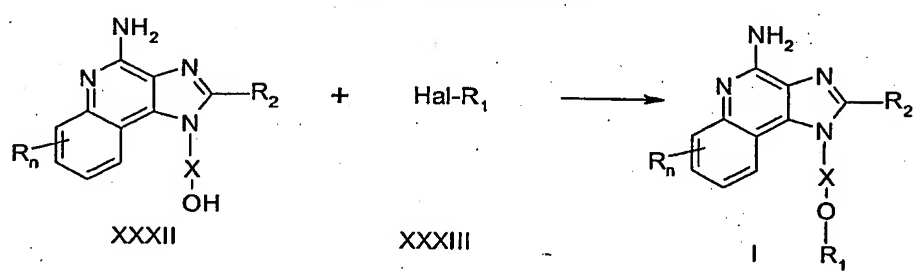
HO-X-O-R4-NH2
(1)
HO-X-O-R4-NH-BOC
XXIII
XXIV
(2)
XXV
(3a)
N3-X-O-R4-NH-BOC
XXVI
(3b)
(4)
N3-X-O-R4-N(BOC)-R7
XXVII
H2N-X-O-R4-N(BOC)-R7
XXVIII
XXIX
(5)
XXX
(6)
XXXI
(7)
XVIII
(8)
XIX
(9)
XX
(10)
XXI
(11)
XXII

Compounds of the invention can be prepared according to Reaction Scheme IV where R, $R_1$, $R_2$, X and n are as defined above

In Reaction Scheme IV a 4-amino-1*H*-imidazo[4,5-*c*]quinolin- 1-yl alcohol of Formula XXXII is alkylated with a halide of Formula XXXIII to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The alcohol of Formula XXXII is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form an alkoxide. The halide is then added to the reaction mixture. The reaction can be carried out at ambient temperature or with gentle heating (~50°C) if desired. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Many compounds of Formula XXXII are known, see for example Gerster, U.S. Patent No. 4,689,338 and Gerster et. al., U.S. Patent No. 5,605,899, the disclosures of which are incorporated by reference herein; others can readily be prepared using known synthetic routes, see for example, Andre et. al, U.S. Patent No. 5,578,727; Gerster, U.S. Patent No. 5,175,296; Nikolaides et al., U.S. Patent No. 5,395,937; and Gerster et. al., U.S. Patent No. 5,741,908, the disclosures of which are incorporated by reference herein. Many halides of Formula XXXIII are commercially available; others can be readily prepared using known synthetic methods.

Reaction Scheme IV



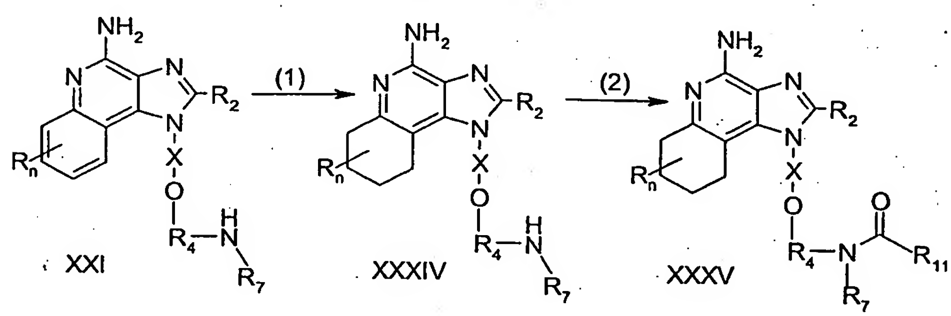

Compounds of the invention can be prepared according to Reaction Scheme V where R, $R_2$, $R_4$, $R_7$, $R_{11}$, X and n are as defined above.

In step (1) of Reaction Scheme V a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXI is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIV. Preferably the reduction is carried out by suspending or

dissolving a compound of Formula XXI in trifluoroacetic acid, adding a catalytic amount of platinum (IV) oxide, and then hydrogenating. The reaction can be conveniently carried out in a Parr apparatus.

Step (2) is carried out in the same manner as step (7) of Reaction Scheme II to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXV which is a subgenus of Formula II. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V

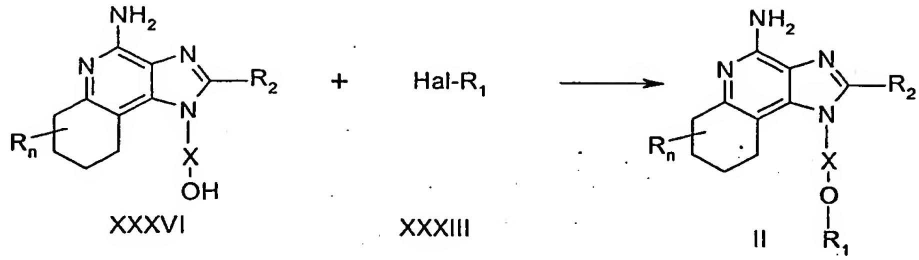



Compounds of the invention can be prepared according to Reaction Scheme VI where R, $R_1$, $R_2$, X and n are as defined above.

In Reaction Scheme VI a 4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula XXXVI is alkylated with a halide of Formula XXXIII to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula II. The alcohol of Formula XXXVI is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form an alkoxide. The halide is then added to the reaction mixture. The reaction can be carried out at ambient temperature or with gentle heating (~50°C) if desired. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Many 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolines of Formula XXXVI are known, see for example, Nikolaides et al., U.S. Patent No. 5,352,784; others can be prepared using known synthetic methods, see for example, Lindstrom, U.S. Patent No. 5,693,811; the disclosures of which are incorporated by reference herein.

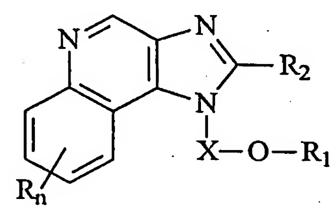
Reaction Scheme VI




XXXVI XXXIII II

The invention also provides novel compounds useful as intermediates in the synthesis of the compounds of Formulas (I) and (II). These intermediate compounds have the structural Formulas (III) – (V), described in more detail below.

One class of intermediate compounds has Formula (III):




(III)

wherein: **X** is $-CHR_5-$, $-CHR_5$-alkyl-, or $-CHR_5$-alkenyl-;

**$R_1$** is selected from the group consisting of:

$-R_4-CR_3-Z-R_6-$alkyl;

$-R_4-CR_3-Z-R_6-$alkenyl;

$-R_4-CR_3-Z-R_6-$aryl;

$-R_4-CR_3-Z-R_6-$heteroaryl;

$-R_4-CR_3-Z-R_6-$heterocyclyl;

$-R_4-CR_3-Z-H$;

$-R_4-NR_7-CR_3-R_6-$alkyl;

$-R_4-NR_7-CR_3-R_6-$alkenyl;

$-R_4-NR_7-CR_3-R_6-$aryl;

-$R_4$–$NR_7$–$CR_3$–$R_6$–heteroaryl;

-$R_4$–$NR_7$–$CR_3$–$R_6$–heterocyclyl; and

-$R_4$–$NR_7$ –$CR_3$–$R_8$;

each **Z** is independently –$NR_5$–, –O–, or –S–;

**$R_2$** is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-CO-$N(R_5)_2$;

-CO-$C_{1-10}$ alkyl;

-CO-O-$C_{1-10}$ alkyl;

-$N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each **$R_3$** is =O or =S;

each **$R_4$** is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **$R_5$** is independently H or $C_{1-10}$ alkyl;

**$R_6$** is a bond, or is alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

**$R_7$** is H, $C_{1-10}$ alkyl, or arylalkyl; or $R_4$ and $R_7$ can join to form a ring;

**$R_8$** is H or $C_{1-10}$ alkyl; or $R_7$ and $R_8$ can join to form a ring;

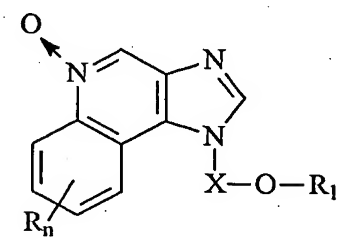
each **Y** is independently –O– or $-S(O)_{0-2}-$;

**n** is 0 to 4; and

each **R** present is independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{1-10}$ alkoxy, hydroxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediates is described by formula (IV):



(IV)

wherein: **X** is $-CHR_5-$, $-CHR_5$-alkyl-, or $-CHR_5$-alkenyl-;

**$R_1$** is selected from the group consisting of:

$-R_4-CR_3-Q-R_6$—alkyl;

$-R_4-CR_3-Q-R_6$—alkenyl;

$-R_4-CR_3-Q-R_6$—aryl;

$-R_4-CR_3-Q-R_6$—heteroaryl;

$-R_4-CR_3-Q-R_6$—heterocyclyl;

$-R_4-CR_3-Q-H$;

$-R_4-NR_5-CR_3-R_6$—alkyl;

$-R_4-NR_5-CR_3-R_6$—alkenyl;

$-R_4-NR_7-CR_3-R_6$—aryl;

$-R_4-NR_7-CR_3-R_6$—heteroaryl;

$-R_4-NR_7-CR_3-R_6$-heterocyclyl; and

$-R_4-NR_5-CR_3-R_8$;

each **Q** is independently $-NR_5-$ or $-O-$;

each $\mathbf{R_3}$ is =O or =S;

each $\mathbf{R_4}$ is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each $\mathbf{R_5}$ is independently H or $C_{1-10}$ alkyl;

$\mathbf{R_6}$ is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

$\mathbf{R_7}$ is H, $C_{1-10}$ alkyl, or arylalkyl; or $R_4$ and $R_7$ can join to form a ring;

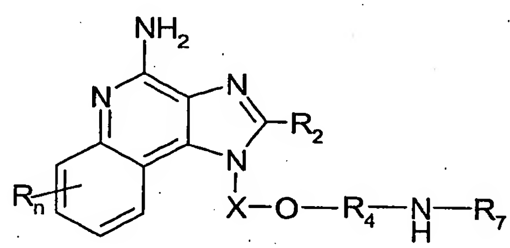
$\mathbf{R_8}$ is H or $C_{1-10}$ alkyl; or $R_4$ and $R_7$ can join to form a ring;

**n** is 0 to 4; and

each **R** present is independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{1-10}$ alkoxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

An additional class of intermediate compounds has the formula (V):




(V)

wherein: **X** is $-CHR_5-$, $-CHR_5$-alkyl-, or $-CHR_5$-alkenyl-;

$\mathbf{R_2}$ is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_5)_2$;

$-CO-N(R_5)_2$;

$-CO-C_{1-10}$ alkyl;

$-CO-O-C_{1-10}$ alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each $\mathbf{R_4}$ is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

$\mathbf{R_7}$ is H, $C_{1-10}$ alkyl,or arylalkyl; or $R_4$ and $R_7$ can join to form a ring;

each **Y** is independently –O– or $-S(O)_{0-2}-$;

**n** is 0 to 4; and

each **R** present is independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{1-10}$ alkoxy, hydroxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably

have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl and adamantyl.

In addition, the alkyl and alkenyl portions of –X-groups can be unsubstituted or substituted by one or more substituents, which substituents are selected from the groups consisting of alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, and the like.

The aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, aroyloxy, aroylthio,

aroylamino, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If any other groups are identified as being "substituted" or "optionally substituted", then those groups can also be substituted by one or more of the above enumerated substituents.

Certain substituents are generally preferred. For example, preferred $R_1$ groups include $—R_4—CR_3—Z—R_6—$alkyl and $—R_4—CR_3—Z—R_6—$aryl, wherein the alkyl and aryl groups can be unsubstituted or substituted; $R_3$ is preferably =O; $R_4$ is preferably ethylene or n-butylene; and Z is preferably $—NR_5—$. Preferably no R substituents are present (i.e., n is 0). Preferred $R_2$ groups include alkyl groups having 1 to 4 carbon atoms (i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and cyclopropylmethyl), methoxyethyl, and ethoxymethyl. For substituted groups such as substituted alkyl or substituted aryl groups, preferred substituents include halogen, nitrile, methoxy, trifluoromethyl, and trifluoromethoxy. One or more of these preferred substituents, if present, can be present in the compounds of the invention in any combination.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg, of the compound to the subject. Any of the conventional dosage forms may be used, such as tablets, lozenges, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and tumors. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal.

Certain compounds of the invention have been found to preferentially induce the expression of IFN-α in a population of hematopoietic cells such as PBMCs (peripheral

blood mononuclear cells) containing pDC2 cells (precursor dendritic cell-type 2) without concomitant production of significant levels of inflammatory cytokines.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulates secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, although there is not believed to be any direct effect on T cells or direct induction of T cell cytokines, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds. This activity means that the compounds are useful in the treatment of diseases where upregulation of the Th1 response and/or downregulation of the Th2 response is desired. In view of the ability of compounds of the invention to inhibit the Th2 immune response, the compounds are expected to be useful in the treatment of atopic diseases, e.g., atopic dermatitis, asthma, allergy, allergic rhinitis; systemic lupus erythematosis; as a vaccine adjuvant for cell mediated immunity; and possibly as a treatment for recurrent fungal diseases and chlamydia.

The immune response modifying effects of the compounds make them useful in the treatment of a wide variety of conditions. Because of their ability to induce the production of cytokines such as IFN-α and/or TNF-α, the compounds are particularly useful in the treatment of viral diseases and tumors. This immunomodulating activity suggests that compounds of the invention are useful in treating diseases such as, but not limited to, viral diseases including genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Virus Type I and Type II; molluscum contagiosum; varriola major; HIV; CMV; VZV; rhinovirus; adenovirus; influenza; and para-influenza; intraepithelial neoplasias such as cervical intraepithelial neoplasia; human papillomavirus (HPV) and associated neoplasias; fungal diseases, e.g. candida, aspergillus, and cryptococcal meningitis; neoplastic diseases, e.g., basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous

leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases, e.g. pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; and bacterial infections, e.g., tuberculosis, and mycobacterium avium. Additional diseases or conditions that can be treated using the compounds of the invention include actinic keratosis; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; alopecia areata; the inhibition of Keloid formation after surgery and other types of post-surgical scars. In addition, these compounds could enhance or stimulate the healing of wounds, including chronic wounds. The compounds may be useful for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-$\alpha$, TNF-$\alpha$, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg.

The invention is further described by the following examples, which are provided for illustration only and are not intended to be limiting in any way.

In the examples below some of the compounds were purified using semi-preparative HPLC. Two different methods were used and they are described below.

Method A

This method used a A-100 Gilson-6 equipped with 900 Series Intelligent Interface. The semi-prep HPLC fractions were analyzed by LC-APCI/MS and the appropriate fractions were combined and lyophilized to provide the trifluoroacetate salt of the desired compound.

Column: column Microsorb C18, 21.4 x 250 mm, 8 micron particle size, 60 Å pore; flow rate: 10 mL/min.; gradient elution from 2-95% B in 25 min., hold at 95% B for 5 min., where A=0.1 % trifluoroacetic acid/water and B=0.1% trifluoroacetic acid/acetonitrile; peak detection at 254 nm for triggering fraction collection.

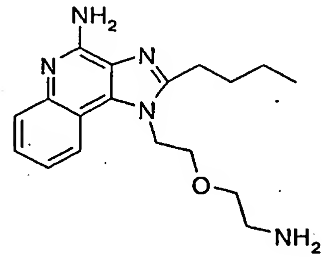
Method B

This method used a Waters Fraction Lynx automated purification system. The semi-prep HPLC fractions were analyzed using a Micromass LC-TOFMS and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. The structure was confirmed by $^{1}H$ NMR spectroscopy.

Column: Phenomenex Luna C18(2), 10 x 50 mm, 5 micron particle size, 100Å pore; flow rate: 25 mL/min.; gradient elution from 5-65% B in 4 min., then 65 to 95 % B in 0.1 min, then hold at 95% B for 0.4 min., where A=0.05 % trifluoroacetic acid/water and B=0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering.

Example 1

1-[2-(2-aminoethoxy)ethyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine




Part A

A solution of 2-(2-aminoethoxy)ethanol (29.0 g, 0.276 mol) in 180 mL of tetrahydrofuran (THF), under $N_2$, was cooled to 0°C and treated with 140 mL of 2N NaOH solution. A solution of di-*tert*-butyl dicarbonate (60.2 g, 0.276 mol) in 180 mL of THF was then added dropwise over 1 h to the rapidly stirred solution. The reaction mixture was then allowed to warm to room temperature and was stirred an additional 18 h. The THF was then removed under reduced pressure and the remaining aqueous slurry was brought to pH 3 by addition of 150 mL of 1M $H_2SO_4$ solution. This was then extracted with ethyl acetate (300 mL, 100 mL) and the combined organic layers were washed with $H_2O$ (2X) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give *tert*-butyl 2-(2-hydroxyethoxy)ethylcarbamate as a colorless oil (47.1 g).

Part B

A rapidly stirred solution of *tert*-butyl 2-(2-hydroxyethoxy)ethylcarbamate (47.1 g, 0.230 mol) in 1 L of anhydrous $CH_2Cl_2$ was cooled to 0°C under $N_2$ and treated with triethylamine (48.0 mL, 0.345 mol). Methanesulfonyl chloride (19.6 mL, 0.253 mol) was then added dropwise over 30 min. The reaction mixture was then allowed to warm to room temperature and was stirred an additional 22 h. The reaction was quenched by addition of 500 mL saturated $NaHCO_3$ solution and the organic layer was separated. The organic phase was then washed with $H_2O$ (3 X 500 mL) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give 2-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}ethyl methanesulfonate as a brown oil (63.5 g).

Part C

A stirred solution of 2-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}ethyl methanesulfonate (63.5 g, 0.224 mol) in 400 mL of N,N-dimethylformamide (DMF) was

treated with $NaN_3$ (16.1 g, 0.247 mol) and the reaction mixture was heated to 90°C under $N_2$. After 5 h, the solution was cooled to room temperature and treated with 500 mL of cold $H_2O$. The reaction mixture was then extracted with $Et_2O$ (3 X 300 mL). The combined organic extracts were washed with $H_2O$ (4 X 100 mL) and brine (2 X 100 mL). The organic portion was dried over $MgSO_4$ and concentrated to give 52.0 g of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate as a light brown oil.

Part D

A solution of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate (47.0 g, 0.204 mol) in MeOH was treated with 4 g of 10% Pd on carbon and shaken under $H_2$ (3 $Kg/cm^2$) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 35.3 g of crude *tert*-butyl 2-(2-aminoethoxy)ethylcarbamate as a colorless liquid that was used without further purification.

Part E

A stirred solution of 4-chloro-3-nitroquinoline (31.4 g, 0.151 mol) in 500 mL of anhydrous $CH_2Cl_2$, under $N_2$, was treated with triethylamine (43 mL, 0.308 mol) and *tert*-butyl 2-(2-aminoethoxy)ethylcarbamate (0.151 mol). After stirring overnight, the reaction mixture was washed with $H_2O$ (2 X 300 mL) and brine (300 mL). The organic portion was dried over $Na_2SO_4$ and concentrated to give a bright yellow solid. Recrystallization from ethyl acetate/hexanes gave 43.6 g of *tert*-butyl 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethylcarbamate as bright yellow crystals.

Part F

A solution of *tert*-butyl 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethylcarbamate (7.52 g, 20.0 mmol) in toluene was treated with 1.5 g of 5% Pt on carbon and shaken under $H_2$ (3 $Kg/cm^2$) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 6.92 g of crude *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate as a yellow syrup.

Part G

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (3.46 g, 10.0 mmol) in 50 mL of toluene was treated with triethylorthovalerate (2.5 mL, 14.5 mmol) and the reaction mixture was heated to reflux. A 25 mg portion of pyridinium hydrochloride was then added and refluxing was continued for 4 h. The reaction was then concentrated to dryness under reduced pressure.

The residue was dissolved in 50 mL of $CH_2Cl_2$ and washed with saturated $NaHCO_3$, $H_2O$ and brine. The organic portion was dried over $Na_2SO_4$ and concetrated to give a green oil. The green oil was dissolved in 50 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 4.12 g of *tert*-butyl 2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a yellow oil.

Part H

A solution of *tert*-butyl 2-[2-(2-butyl-1H-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethylcarbamate (4.12 g, 10.0 mmol) in 50 mL of $CH_2Cl_2$ was treated with 3-chloroperoxybenzoic acid (MCPBA, 77%, 2.5 g, 11.2 mmol). After stirring for 5 h, the reaction mixture was treated with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed with $H_2O$ and brine then dried over $Na_2SO_4$ and concentrated to give 3.68 g of *tert*-butyl 2-[2-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part I

A solution of *tert*-butyl 2-[2-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (3.68 g, 8.60 mmol) in 100 mL of 1,2-dichloroethane was heated to 80 °C and treated with 10 mL of concentrated $NH_4OH$ solution. To the rapidly stirred solution was added solid p-toluenesulfonyl chloride (1.87 g, 9.81 mmol) over a 10 min. period. The reaction mixture was then sealed in a pressure vessel and heating was continued for 2 h. The reaction mixture was then cooled and treated with 100 mL of $CH_2Cl_2$. The reaction mixture was then washed with $H_2O$, 1% $Na_2CO_3$ solution (3X) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give 3.68 g of *tert*-butyl 2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

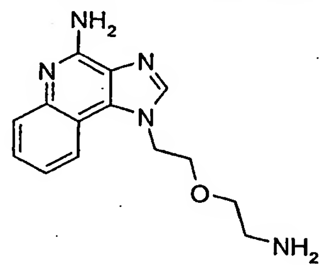
Part J

T*ert*-butyl 2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (3.68 g, 8.60 mmol) was suspended in 20 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 3 h, the reaction mixture was concentrated to give a solid. The solid was triturated with hot EtOH (50 mL) and filtered to give 2.90 g of the product as the hydrochloride salt. The free base was made by dissolving the hydrochloride salt in 50 mL of $H_2O$ and treating with 5 mL of concentrated $NH_4OH$. The aqueous suspension was extracted with $CH_2Cl_2$ (3 X 50 mL). The

combined organic layers were dried over $Na_2SO_4$ and concentrated to give 1-[2-(2-aminoethoxy)ethyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.
MS 328 $(M + H)^+$;
$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J$ = 8.3 Hz, 1 H); 7.83 (d, $J$ = 8.4 Hz, 1 H); 7.50 (m, 1 H); 7.30 (m, 1 H); 5.41 (s, 2 H); 4.69 (t, $J$ = 5.6 Hz, 2 H); 3.93 (t, $J$ = 5.6 Hz, 2 H); 3.39 (t, $J$ = 5.1 Hz, 2 H); 2.97 (t, $J$ = 7.9 Hz, 2 H); 2.76 (t, $J$ = 5.1 Hz, 2 H); 1.89 (m, 2 H); 1.52 (m, 2 H); 1.26 (br s, 2 H); 1.01 (t, $J$ = 7.3 Hz, 3 H).

Example 2

1-[2-(2-aminoethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine




Part A

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (6.92 g, 20.0 mmol) in 100 mL of toluene was treated with triethylorthoformate (4.65 mL, 28.0 mmol) and the reaction mixture was heated to reflux. A 100 mg portion of pyridinium hydrochloride was then added and refluxing was continued for 2 h. The reaction was then concentrated to dryness under reduced pressure. The residue was dissolved in 200 mL of $CH_2Cl_2$ and washed with saturated $NaHCO_3$, $H_2O$ and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give a green oil. The green oil was dissolved in 200 mL of hot MeOH and treated with 10 g of activated charcoal. The hot solution was filtered and concentrated to give 5.25 g of *tert*-butyl 2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light yellow syrup.

Part B

A solution of *tert*-butyl 2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (5.25 g, 14.7 mmol) in 200 mL of $CH_2Cl_2$ was treated with

MCPBA (77%, 3.63 g, 16.3 mmol). After stirring overnight, the reaction mixture was treated with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed with $H_2O$ and brine then dried over $Na_2SO_4$ and concentrated to give 4.60 g of *tert*-butyl 2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part C

A solution of *tert*-butyl 2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (4.60 g, 12.4 mmol) in 150 mL of 1,2-dichloroethane was heated to 80 °C and treated with 10 mL of concentrated $NH_4OH$ solution. To the rapidly stirred solution was added solid p-toluenesulfonyl chloride (2.71 g, 14.2 mmol) over a 10 min period. The reaction mixture was treated with an additional 2 mL of concentrated $NH_4OH$ solution and then sealed in a pressure vessel and heating was continued for 3 h. The reaction mixture was then cooled and treated with 100 mL of $CH_2Cl_2$. The reaction mixture was then washed with $H_2O$, 1% $Na_2CO_3$ solution (3X) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give 4.56 g of *tert*-butyl 2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part D

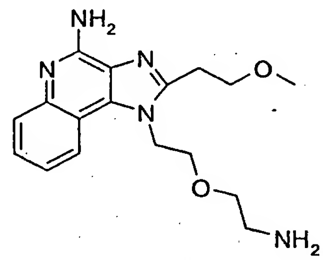
*Tert*-butyl 2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (4.56 g, 12.3 mmol) was dissolved in 100 mL of EtOH and treated with 30 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 3 h, the reaction mixture was concentrated to give a solid. The solid was triturated with hot EtOH (100 mL) and filtered to give the product as the hydrochloride salt. The free base was made by dissolving the hydrochloride salt in 50 mL of $H_2O$ and treating with 5 mL of concentrated $NH_4OH$. The aqueous suspension was extracted with $CH_2Cl_2$ (5 X 50 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated to give 1.35 g of 1-[2-(2-aminoethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.

MS 272 $(M + H)^+$;

$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.98 (d, $J$ = 8.2 Hz, 1 H); 7.88 (s, 1 H); 7.84 (d, $J$ = 8.4 Hz, 1 H); 7.54 (m, 1 H); 7.32 (m, 1 H); 5.43 (s, 2 H); 4.74 (t, $J$ = 5.2 Hz, 2 H); 3.97 (t, $J$ = 5.2 Hz, 2 H); 3.42 (t, $J$ = 5.1 Hz, 2 H); 2.78 (t, $J$ = 5.1 Hz, 2 H); 1.10 (br s, 2 H).

Example 3

1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (10.2 g, 29.5 mmol) in 250 mL of anhydrous $CH_2Cl_2$ was cooled to 0°C and treated with triethylamine (4.18 mL, 30.0 mmol). Methoxypropionyl chloride (3.30 mL, 30.3 mmol) was then added dropwise over 5 min. The reaction was then warmed to room temperature and stirring was continued for 1 h. The reaction mixture was then concentrated under reduced pressure to give an orange solid. This was dissolved in 250 mL of EtOH and 12.5 mL of triethylamine was added. The mixture was heated to reflux and stirred under $N_2$ overnight. The reaction was then concentrated to dryness under reduced pressure and treated with 300 mL of $Et_2O$. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give a brown solid. The solid was dissolved in 200 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 11.1 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as a yellow syrup.

Part B

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.22 g, 24.7 mmol) in 250 mL of $CHCl_3$ was treated with MCPBA (77%, 9.12 g, 40.8 mmol). After stirring 30 min, the reaction mixture was washed with 1% $Na_2CO_3$ solution (2 X 75 mL) and brine. The organic layer was then dried over $Na_2SO_4$ and concentrated to give 10.6 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as an orange foam that was used without further purification.

Part C

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.6 g, 24.6 mmol) in 100 mL of 1,2-dichloroethane was heated to 60°C and treated with 10 mL of concentrated $NH_4OH$ solution. To the rapidly stirred solution was added solid p-toluenesulfonyl chloride (7.05 g, 37.0 mmol) over a 10 min period. The reaction mixture was treated with an additional 1 mL concentrated $NH_4OH$ solution and then sealed in a pressure vessel and heating was continued for 2 h. The reaction mixture was then cooled and treated with 100 mL of $CHCl_3$. The reaction mixture was then washed with $H_2O$, 1% $Na_2CO_3$ solution (2X) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give 10.6 g of *tert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as a brown foam.

Part D

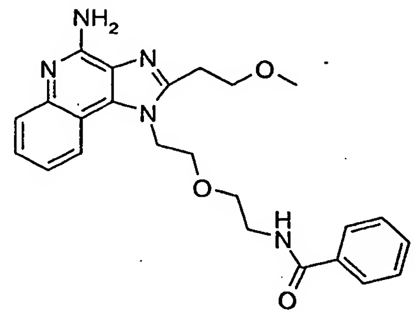
T*ert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.6 g, 24.6 mmol) was treated with 75 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 1.5 h, the reaction mixture was cooled and filtered to give a gummy solid. The solid was washed EtOH and $Et_2O$ and dried under vacuum to give the hydrochloride salt as a light brown solid. The free base was made by dissolving the hydrochloride salt in 50 mL of $H_2O$ and treating with 10% NaOH solution. The aqueous suspension was then concentrated to dryness and the residue was treated with $CHCl_3$. The resulting salts were removed by filtration and the filtrate was concentrated to give 3.82 g of 1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-4-amine as a tan powder.

MS 330 $(M + H)^+$;

$^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.10 (d, $J$ = 8.1 Hz, 1 H); 7.66 (d, $J$ = 8.2 Hz, 1 H); 7.40 (m, 1 H); 7.25 (m, 1 H); 6.88 (br s, 2 H); 4.78 (t, $J$ = 5.4 Hz, 2 H); 3.89 (t, $J$ = 4.8 Hz, 2 H); 3.84 (t, $J$ = 6.9 Hz, 2 H); 3.54 (t, $J$ = 5.4 Hz, 2 H); 3.31 (s, 3 H); 3.23 (t, $J$ = 6.6 Hz, 2 H); 2.88 (t, $J$ = 5.3 Hz, 2 H).

Example 4

*N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)benzamide



1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (750 mg, 2.28 mmol) was dissolved in 35 mL of anhydrous $CH_2Cl_2$ and cooled to 0 °C under $N_2$. To the stirred solution were added $Et_3N$ (0.35 mL, 2.50 mmol) and benzoyl chloride (260 μL, 2.28 mmol) and the reaction was allowed to warm to room temperature over 2.5 h. The reaction mixture was then quenched by addition of saturated $NaHCO_3$ solution (30 mL) and $CH_2Cl_2$ (30 mL). The organic layer was separated and washed with $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure to give a tan foam. Mass spectral analysis showed the presence of some bis-amide in addition to the desired product. The tan foam was treated with 1N aqueous HCl solution (50 mL) at 100 °C for 5 h. HPLC analysis showed that all of the bis-amide had been converted to the desired product. The reaction was cooled to room temperature and treated with 10% NaOH until the pH~11. The mixture was extracted with $CHCl_3$ (3 X 30 mL). The combined organic extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure to give a yellow solid. Purification by column chromatography ($SiO_2$, 5-10% MeOH/$CHCl_3$) gave 100 mg of *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)benzamide as a white powder. m.p. 184-187 °C;

MS 434 $(M + H)^+$;

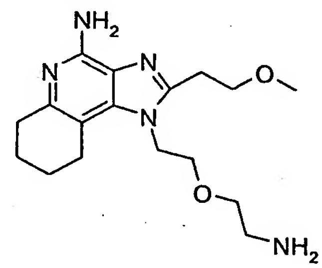
$^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.40 (m, 1 H); 8.06 (d, $J$ = 8.3 Hz, 1 H); 7.76-7.74 (m, 2 H); 7.60 (d, $J$ = 7.8 Hz, 1 H); 7.54-7.37 (m, 4 H); 7.19 (t, $J$ = 7.3 Hz, 1 H); 6.48 (s, 2 H);

4.79-4.72 (m, 2 H); 3.91-3.84 (m, 2 H); 3.78 (t, $J$ = 6.9 Hz, 2 H); 3.48 (t, $J$ = 5.5 Hz, 2 H); 3.25 (s, 3 H); 3.20 (t, $J$ = 6.3 Hz, 2 H);

$^{13}C$ (75 MHz, DMSO-$d_6$) δ 166.7, 152.0, 151.9, 145.2, 134.8, 132.7, 131.4, 128.6, 127.4, 126.7, 121.4, 120.5, 115.1, 70.4, 69.4, 69.2, 58.4, 45.5, 27.6.

Example 5

1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine



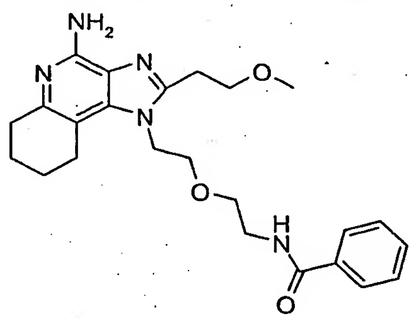
1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (10.0 g, 27.3 mmol) was dissolved in 50 mL of trifluoroacetic acid and treated with $PtO_2$ (1.0 g). The reaction mixture was shaken under $H_2$ (3 Kg/cm$^2$). After 4 d, an additional 0.5 g of $PtO_2$ was added and hydrogenation was continued for an additional 3 d. The reaction was then filtered through Celite and concentrated under reduced pressure to give a brown oil. The yellow oil was dissolved in 200 mL of $H_2O$ then made basic (pH~11) by addition of 10% NaOH solution. This was then extracted with $CHCl_3$ (5 X 75 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated to give 5.17 g of 1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan solid.

MS 334 $(M + H)^+$;

$^1H$ NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 2 H); 4.49 (t, $J$ = 5.4 Hz, 2 H); 3.84 (t, $J$ = 6.6 Hz, 2 H); 3.71 (t, $J$ = 5.4 Hz, 2 H), 3.36 (t, $J$ = 5.2 Hz, 2 H); 3.51 (s, 3 H); 3.15 (t, $J$ = 6.6 Hz, 2 H); 2.95 (m, 2 H); 2.82 (m, 2 H); 2.76 (t, $J$ = 5.1 Hz, 2 H); 1.84 (m, 4 H), 1.47 (br s, 2 H).

Example 6

*N*-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)benzamide



1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.00 g, 3.00 mmol) was dissolved in 30 mL of anhydrous $CH_2Cl_2$ and cooled to 0 °C under $N_2$. To the stirred solution were added $Et_3N$ (0.84 mL, 6.00 mmol) and benzoyl chloride (348 μL, 3.00 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then quenched by addition of saturated $NaHCO_3$ solution (30 mL). The organic layer was separated and washed with $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure to give a yellow oil. The oil was dissolved in a minimum amount of hot MeOH and then treated with $Et_2O$ (50 mL) which caused a white percipitate to form. The solid was isolated by filtration and dried under vacuum to give 476 mg of N-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)benzamide as a white powder. m.p. 141-143°C;

MS 438 $(M + H)^+$;

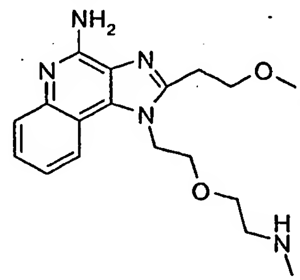
$^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8.36 (t, $J$ = 5.4 Hz, 1 H); 7.78-7.76 (m, 2 H); 7.54-7.42 (m, 3 H); 5.68 (s, 2 H); 4.43 (t, $J$ = 5.4 Hz, 2 H); 3.75-3.69 (m, 4 H); 3.48 (t, $J$ = 6.0 Hz, 2 H); 3.37 (t, $J$ = 5.5 Hz, 2 H); 3.24 (s, 3 H); 3.07 (t, $J$ = 6.9 Hz, 2 H); 2.91 (m, 2 H); 2.63 (m, 2 H); 1.70 (m, 4 H);

$^{13}C$ (75 MHz, DMSO-$d_6$) δ 166.7, 151.3, 149.3, 146.2, 138.5, 134.8, 131.4, 128.6, 127.5, 124.9, 105.6, 70.5, 70.5, 69.3, 58.4, 44.6, 32.7, 27.6, 23.8, 23.0, 23.0.

Anal. Calcd for $C_{24}H_{31}N_5O_3$: %C, 65.88; %H, 7.14; %N, 16.01. Found: %C, 65.55; %H, 7.15; %N, 15.87.

Example 7

2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Sodium hydride (60% oil dispersion, 9.1 g, 228 mmol) was placed in a round bottom flask and washed with hexanes (3X) under $N_2$. The dried sodium hydride was treated with 800 mL of anhydrous THF. A solution of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate (41.9 g, 182 mmol) in 200 mL of THF was then added to the stirred sodium hydride solution over 40 min. After addition was complete, the reaction was stirred an additional 20 min followed by addition of methyl iodide (13.6 mL, 218 mmol). After stirring overnight, the reaction was quenched with 300 mL of saturated $NaHCO_3$ solution. The reaction mixture was then treated with 200 mL of $H_2O$ and 1 L of $Et_2O$. The organic phase was separated and washed with $H_2O$ and brine. The organic portion was then dried over $MgSO_4$ and concentrated under reduced pressure to give 41.9 g of *tert*-butyl 2-(2-azidoethoxy)ethyl(methyl)carbamate as a yellow liquid.

Part B

A solution *tert*-butyl 2-(2-azidoethoxy)ethyl(methyl)carbamate (41.9 g, 170 mmol) in 600 mL of MeOH was treated with 2.5 g of 10% Pd on carbon and shaken under $H_2$ (3 Kg/cm$^2$) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 37.2 g of crude *tert*-butyl 2-(2-aminoethoxy)ethyl(methyl)carbamate as a light yellow liquid.

Part C

A stirred solution of 4-chloro-3-nitroquinoline (32.3 g, 155 mmol) in 400 mL of anhydrous $CH_2Cl_2$, under $N_2$, was treated with triethylamine (43.1 mL, 310 mmol) and

*tert*-butyl 2-(2-aminoethoxy)ethyl(methyl)carbamate (37.2 g, 171 mmol). After stirring overnight, the reaction mixture was washed with $H_2O$ (2 X 300 mL) and brine (300 mL). The organic portion was dried over $Na_2SO_4$ and concentrated to give a brown oil. Column chromatography ($SiO_2$, 33% ethyl acetate/hexanes-67% ethyl acetate/hexanes) gave 46.7 g of *tert*-butyl methyl(2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl)carbamate as a yellow solid.

Part D

A solution of *tert*-butyl methyl(2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl)carbamate (6.56 g, 16.8 mmol) in 75 mL of toluene was treated with 0.5 g of 5% Pt on carbon and shaken under $H_2$ (3 Kg/cm$^2$) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 6.8 g of crude *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethyl(methyl)carbamate as an orange syrup which was carried on without further purification.

Part E

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethyl(methyl)carbamate (6.05 g, 16.8 mmol) in 200 mL of anhydrous $CH_2Cl_2$ was cooled to 0 °C and treated with triethylamine (2.40 mL, 17.2 mmol). Methoxypropionyl chloride (1.72 mL, 17.2 mmol) was then added dropwise over 5 min. The reaction was then warmed to room temperature and stirring was continued for 3 h. The reaction mixture was then concentrated under reduced pressure to give an orange solid. This was dissolved in 200 mL of EtOH and 7.2 mL of triethylamine was added. The mixture was heated to reflux and stirred under $N_2$ overnight. The reaction was then concentrated to dryness under reduced pressure and treated with 300 mL of $Et_2O$. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give a brown solid. This was dissolved in 300 mL of $CH_2Cl_2$ and washed with $H_2O$ and brine. The organic portion was dried over $Na_2SO_4$ and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 100 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 7.20 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a yellow syrup.

Part F

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (7.20 g, 16.8 mmol) in 200 mL of $CH_2Cl_2$ was treated with MCPBA (77%, 4.32 g, 19.3 mmol). After stirring 6 h, the reaction mixture was treated with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed with $H_2O$ and brine then dried over $Na_2SO_4$ and concentrated to give 7.05 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a light brown solid.

Part G

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (7.05 g, 15.9 mmol) in 100 mL of 1,2-dichloroethane was heated to 80 °C and treated with 5 mL of concentrated $NH_4OH$ solution. To the rapidly stirred solution was added solid p-toluenesulfonyl chloride (3.33 g, 17.5 mmol) over a 10 min period. The reaction mixture was treated with an additional 5 mL concentrated $NH_4OH$ solution and then sealed in a pressure vessel and heating was continued for 4 h. The reaction mixture was then cooled and treated with 100 mL of $CH_2Cl_2$. The reaction mixture was then washed with $H_2O$, 1% $Na_2CO_3$ solution (3X) and brine. The organic portion was dried over $Na_2SO_4$ and concentrated to give 6.50 g of *tert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a brown oil

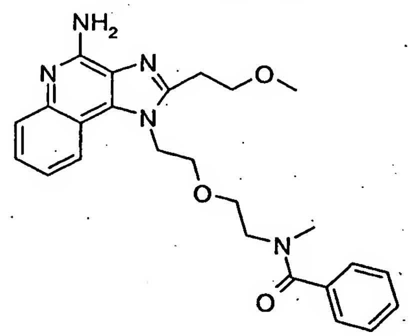
Part H

T*ert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (6.50 g, 14.7 mmol) was dissolved in 100 mL of EtOH and treated with 20 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 6 h, the reaction mixture was cooled and filtered to give a gummy solid. The solid was washed with EtOH and $Et_2O$ and dried under vacuum to give the hydrochloride salt as a light brown powder. The free base was made by dissolving the hydrochloride salt in 50 mL of $H_2O$ and treating with 5 mL of concentrated $NH_4OH$. The aqueous suspension was extracted with $CH_2Cl_2$ (5 X 50 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated to give 3.93 g of 2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder. MS 344 $(M + H)^+$;

$^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ 8.07 (d, $J$ = 7.7 Hz, 1 H); 7.62 (dd, $J$ = 1.0, 8.3 Hz, 1 H); 7.42 (ddd, $J$ = 1.0, 7.1, 8.2 Hz, 1 H); 7.22 (ddd, $J$ = 1.1, 7.1, 8.2 Hz, 1 H); 6.49 (s, 2 H); 4.75 (t, $J$ = 5.1 Hz, 2 H); 3.83 (t, $J$ = 6.8 Hz, 4 H); 3.35 (t, $J$ = 5.6 Hz, 2 H); 3.30 (s, 3 H); 3.21 (t, $J$ = 6.9 Hz, 2 H); 2.45 (t, $J$ = 5.6 Hz, 2 H); 2.12 (s, 3 H).

## Example 8

## *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methylbenzamide



2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.00 g, 2.92 mmol) was dissolved in 30 mL of anhydrous $CH_2Cl_2$ and cooled to 0 °C under $N_2$. To the stirred solution were added $Et_3N$ (0.81 mL, 5.81 mmol) and benzoyl chloride (340 μL, 2.92 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then quenched by addition of saturated $NaHCO_3$ solution (30 mL) and $CH_2Cl_2$ (30 mL). The organic layer was separated and washed with $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography ($SiO_2$, 3% MeOH/$CHCl_3$ saturated with aqueous $NH_4OH$) gave the product as a colorless foam. Crystallization from PrOAc and hexanes gave 540 mg of *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methylbenzamide as a white powder. m.p. 93.5-97.0 °C;

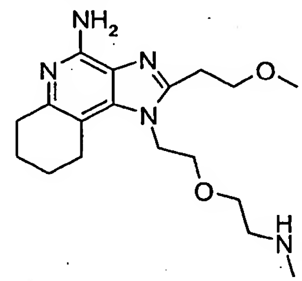
MS 448 $(M + H)^+$;

$^{1}H$ NMR (500 MHz, DMSO-$d_6$, 60 °C) δ 8.04 (d, $J$ = 7.7 Hz, 1 H); 7.63 (dd, $J$ = 0.9, 8.2 Hz, 1 H); 7.42-7.33 (m, 4 H); 7.23-7.19 (m, 3 H); 6.24 (s, 2 H); 4.74 (m, 2 H); 3.86 (m, 2 H); 3.82 (t, $J$ = 6.8 Hz, 2 H); 3.51 (m, 2 H); 3.40 (m, 2 H); 3.29 (s, 3 H); 3.18 (t, $J$ = 6.7 Hz, 2 H); 2.75 (br s, 3 H);

$^{13}C$ NMR (125 MHz, DMSO-$d_6$, 60 °C) δ 152.0, 151.9, 145.3, 137.1, 132.8, 131.3, 129.4, 128.5, 127.0, 126.9, 126.8, 126.6, 121.4, 120.4, 115.3, 70.5, 69.5, 68.8, 58.4, 45.5, 27.8. Anal. Calcd for $C_{25}H_{29}N_5O_3$: %C, 67.09; %H, 6.53; %N, 15.65. Found: %C, 67.08; %H, 6.56; %N, 15.58

## Example 9

2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine



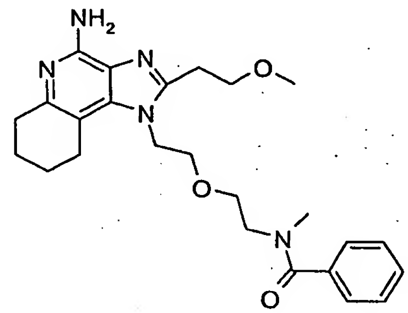
2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (4.22 g, 12.3 mmol) was dissolved in 25 mL of trifluoroacetic acid and treated with $PtO_2$ (0.5 g). The reaction mixture was shaken under $H_2$ (3 Kg/cm$^2$). After 4 d, an additional 0.5 g of $PtO_2$ was added and hydrogenation was continued for an additional 3 d. The reaction was then filtered through Celite and concentrated under reduced pressure to give a yellow oil. The yellow oil was dissolved in 50 mL of $H_2O$ and extracted with 50 mL of $CHCl_3$. The organic portion was removed and discarded. The aqueous portion was then made basic (pH~12) by addition of 10% NaOH solution. This was then extracted with $CHCl_3$ (6 X 50 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated to a brown oil. The brown oil was dissolved in 100 mL of hot MeOH and treated with 1 g of activated charcoal. The hot solution was filtered through Celite and concentrated to dryness. The resulting gummy solid was concentrated several times with $Et_2O$ to give 3.19 g of 2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white powder.

MS 348 $(M + H)^+$;

$^{1}H$ NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 2 H); 4.48 (t, $J$ = 5.7 Hz, 2 H); 3.84 (t, $J$ = 6.7 Hz, 2 H); 3.70 (t, $J$ = 5.7 Hz, 2 H); 3.46 (t, $J$ = 5.1 Hz, 2 H); 3.36 (s, 3 H); 3.14 (t, $J$ = 6.7 Hz, 2 H); 2.96 (m, 2 H); 2.83 (m, 2 H); 2.65 (t, $J$ = 5.1 Hz, 2 H); 2.36 (s, 3 H); 1.85 (m, 4 H).

## Example 10

*N*-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methylbenzamide



2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (750 mg, 2.16 mmol) was dissolved in 20 mL of anhydrous $CH_2Cl_2$ and cooled to 0 °C under $N_2$. To the stirred solution were added $Et_3N$ (0.60 mL, 4.32 mmol) and benzoyl chloride (250 μL, 2.16 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then quenched by addition of saturated $NaHCO_3$ solution (30 mL) and $CH_2Cl_2$ (30 mL). The organic layer was separated and washed with $H_2O$ (3X) and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography ($SiO_2$, 3% MeOH/$CHCl_3$ saturated with aqueous $NH_4OH$) gave the product as a colorless foam. The foam was concentrated from *iso*-propyl alcohol to give an syrup which solidified upon standing. The solid was dried under vacuum to give the 408 mg of N-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-N-methylbenzamide as an off-white powder.

m.p 83.0-87.0 °C ;

MS 452 $(M + H)^+$;

$^{1}H$ NMR (500 MHz, DMSO-$d_6$, 60 °C) δ 7.37 (m, 3 H); 7.23 (m, 2 H); 5.46 (s, 2 H); 4.43(m, 2 H); 3.76 (t, $J$ = 6.8 Hz, 2 H); 3.68 (m, 2 H); 3.50 (m, 2 H); 3.42 (m, 2 H); 3.27

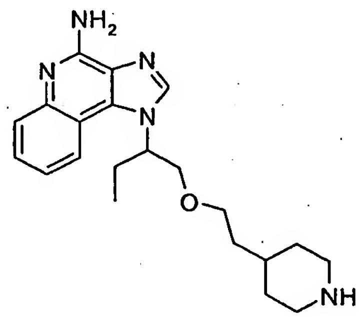
(s, 3 H); 3.05 (t, $J$ = 6.4 Hz, 2 H); 2.92 (m, 2 H); 2.80 (s, 3 H); 2.65 (m, 2 H); 1.74 (m, 4 H);

$^{13}$C NMR (125 MHz, DMSO-$d_6$, 60 °C) δ 150.5, 148.5, 145.8, 137.9, 136.4, 128.7, 127.8, 126.3, 124.5, 105.1, 70.1, 69.8, 68.0, 57.7, 44.0, 32.1, 27.1, 23.2, 22.4, 22.4

Anal. Calcd for $C_{25}H_{33}N_5O_3{\bullet}0.30\ C_3H_8O$: %C, 66.24; %H, 7.60; %N, 14.91. Found: %C, 65.86; %H, 7.81; %N, 15.10.

Example 11

1-{1-[(2-piperidin-4-ylethoxy)methyl]propyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine




Part A

Using the general method of Part A of Example 1, 4-piperidineethanol (10 g, 77.4 mmol) was reacted with di-*tert*-butyl dicarbonate (17.7 g, 81.3 mmol) to provide 13.1 g of *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate as a clear oil.

Part B

Iodine (7.97 g) was added in three portions to a solution of imidazole (3.89 g, 57.1 mmol) and triphenylphosphine (14.98 g, 57.1 mmol) in dichloromethane (350 mL). After 5 minutes a solution of the material from Part A in dichloromethane (70 mL) was added. The reaction mixture was stirred at ambient temperature overnight. More iodine (7.97 g) was added and the reaction was stirred at ambient temperature for 1 hr. The reaction mixture was washed with saturated sodium thiosulfate (2X) and brine, dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide an oily residue. The residue was purified by column chromatography (silica gel eluting with 20% ethyl acetate in hexanes) to provide 15.52 g of *tert*-butyl 4-(2-iodoethyl)piperidine-1-carboxylate as a pale yellow oil.

Part C

Under a nitrogen atmosphere, 2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (6.5 g, 26.9 mmol) was added in three portions to a suspension of sodium hydride (1.4 g of 60%, 35.0 mmol) in anhydrous N,N-dimethylformamide. The reaction mixture was allowed to stir for 45 minutes by which time gas evolution had ceased. *Tert*-butyl 4-(2-iodoethyl)piperidine-1-carboxylate (10.05 g, 29.6 mmol) was added dropwise over a period of 15 minutes. The reaction mixture was allowed to stir at ambient temperature for 2.5 hrs; then it was heated to 100°C and stirred overnight. Analysis by HPLC showed that the reaction was about 35% complete. Saturated ammonium chloride solution was added, the resulting mixture was allowed to stir for 20 minutes and then it was extracted with ethyl acetate (2X). The ethyl acetate extracts were washed with water (2X) and then with brine, combined, dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide a brown oil. The oil was purified by column chromatography (silica gel eluting sequentially with 30% ethyl acetate in hexanes, 50% ethyl acetate in hexanes, and ethyl acetate) to provide 2.2 g of *tert*-butyl 4-{2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate.

Part D

Using the general method of Example 1 Part H, the material from Part C was oxidized to provide *tert*-butyl 4-{2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate as an oil.

Part E

Ammonium hydroxide solution (20 mL) was added to a solution of the material from Part D in dichloromethane (20 mL). A solution of tosyl chloride (0.99 g, 5.2 mmol) in dichloromethane (10 mL) was added over a period of 5 minutes. The resulting biphasic reaction mixture was allowed to stir overnight. The reaction mixture was diluted with chloroform and saturated sodium bicarbonate solution. The layers were separated. The organic layer was dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide a brown glass. This material was purified by column chromatography (silica gel eluting first with 50% ethyl acetate in hexanes and then with ethyl acetate) to provide 1.0 g of *tert*-butyl 4-{2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate as pale yellow glassy foam.

Part F

Under a nitrogen atmosphere, *tert*-butyl 4-{2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate (1.00 g, 2.1 mmol) and 2N ethanolic hydrochloric acid (10 ml, 20 mmol) were combined and the solution was stirred at ambient temperature for 14 hours. The solvent was removed *in vacuo* and the resulting tan solid was dissolved in water. Saturated aqueous sodium carbonate was added until the pH reached 10. After extraction with dichloromethane (3X), the organic fractions were combined, washed with brine, dried ($Na_2SO_4$), filtered, and the majority of the solvent was removed *in vacuo*. Hexane was added to form a precipitate. Vacuum filtration yielded 0.5 g of 1-{1-[(2-piperidin-4-ylethoxy)methyl]propyl}-1*H*-imidazo[4,5-c]quinolin-4-amine as a tan powder.

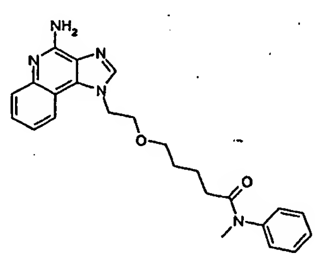
$^1$H-NMR (300MHz, DMSO-$d_6$) : δ 8.34 (bs, 1H), 8.19 (d, J = 8.49Hz, 1H), 7.61 (dd, J = 8.31, 1.13Hz, 1H), 7.45-7.39 (m, 1H), 7.25-7.19 (m, 1H), 6.55 (s, 2H), 5.25-5.15 (m, 1H), 4.00-3.80 (m, 2H), 3.5-3.3 (m, 2H), 2.8-2.64 (m, 2H), 2.22-2.11 (m, 2H), 2.09-1.99 (m, 2H), 1.8-1.63 (bs, 1H), 1.37-1.0 (m, 5H), 0.95-0.7 (m, 5H);

$^{13}$C-NMR (75MHz, DMSO-$d_6$): δ 152.8, 145.8, 140.6, 133.0, 127.8, 127.0, 126.9, 121.3, 121.0, 115.5, 71.8, 68.1, 58.4, 46.1, 36.3, 33.1, 32.7, 24.5, 9.9;

MS (CI) m/e 368.2459 (368.2450 calcd for $C_{21}H_{30}N_5O$).

Example 12

5-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]-N-methyl-N-phenylpentanamide




Using the general method of Parts C and D of Example 11, 2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethanol (0.63 g, 2.9 mmol) and 5-bromo-N-methyl-N-phenylpentanamide (1.3 g, 4.8 mmol) were combined to provide 0.24 g of 5-[2-(5-oxido-1*H*-imidazo[4,5-

*c*]quinolin-1-yl)ethoxy]-N-methyl-N-phenylpentanamide as a colorless oil. The resulting N-oxide product was dissolved in dichloromethane and trichloroacetyl isocyanate (0.11 ml) was added dropwise. The reaction was stirred at room temperature for 2 hours and then the solvent was removed under vacuum. The resulting oil was dissolved in methanol and sodium methoxide (0.2 ml, 25% by weight in methanol) was slowly added. The reaction was maintained overnight and then concentrated under vacuum. Purification by flash column chromatography (silica gel, 9:1 ethyl acetate\methanol) provided 24 mg of 5-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]-N-methyl-N-phenylpentanamide as a white solid.

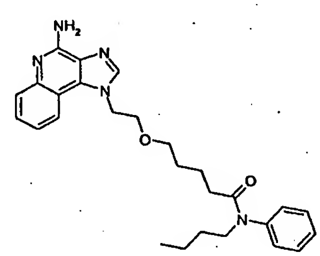
$^1$H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J=8.1 Hz, 1H), 7.83 (m, 2H), 7.52 (dt, J=7.7,1.3 Hz, 1H), 7.41-7.28 (m, 4H), 7.12 (d, J=7.8 Hz, 2H), 5.55 (broad s, 2H), 4.65 (t, J=5.3 Hz, 2H), 3.85 (t, J=5.3 Hz, 2H), 3.31 (t, J=6.3 Hz, 2H), 3.24 (s, 3H), 2.02 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H);

IR (KBr) 3429, 3104, 2946, 2877, 1646, 1595, 1584, 1532, 1496, 1482, 1398, 1360, 1254, 1121, 749, 705 cm$^{-1}$;

MS (EI) m/e 417.2160 (417.2165 calcd for $C_{24}H_{27}N_5O_2$).

## Example 13

5-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]-N-butyl-N-phenylpentanamide



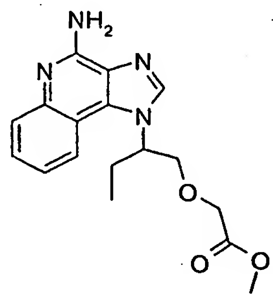
2-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)ethanol and 5-bromo-N-butyl-N-phenylpentanamide were combined and treated according to the general procedure described in Example 12. Purification by flash column chromatography (silica gel, 98:2 ethyl acetate\methanol) provided 5-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]-N-butyl-N-phenylpentamide as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J=8.0 Hz, 1H), 7.87-7.85 (m, 2H), 7.54 (dt, J=7.7,1.1 Hz, 1H), 7.41-7.29 (m, 4H), 7.10 (d, J=7.2 Hz, 2H), 6.20 (broad s, 2H), 4.66 (t,

J=5.2 Hz, 2H), 3.85 (t, J=5.2 Hz, 2H), 3.66 (t, J=7.5 Hz, 2H), 3.31 (t, J=6.2 Hz, 2H), 1.96 (t, J=7.2 Hz, 2H), 1.56-1.25 (m, 8H), 0.88 (t, J=7.2 Hz, 3H);
MS (EI) m/e 459.2631 (459.2634 calcd for $C_{27}H_{33}N_5O_2$).

## Example 14

### Methyl [2-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]acetate

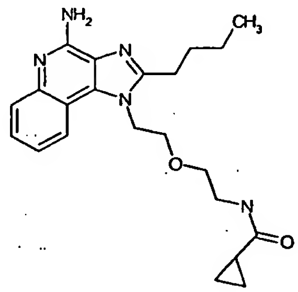
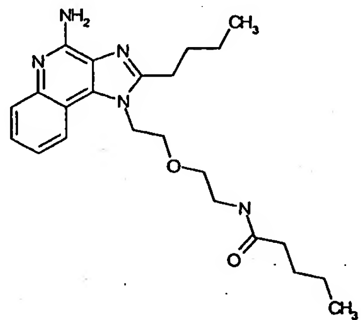
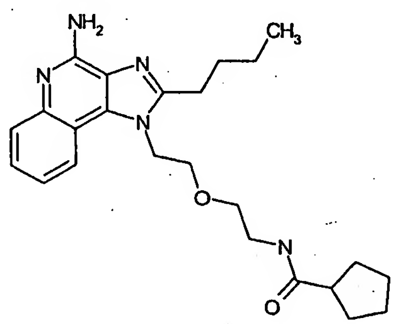
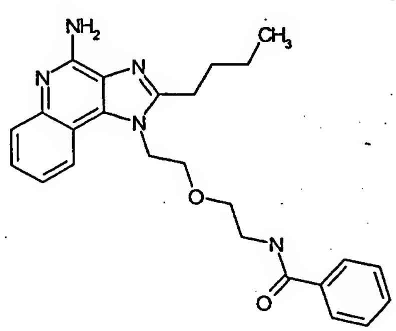


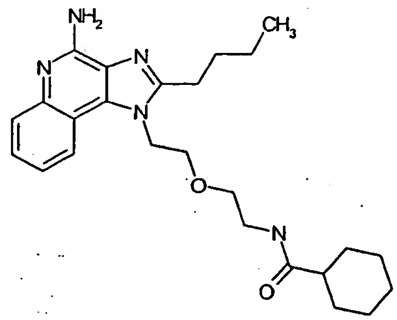
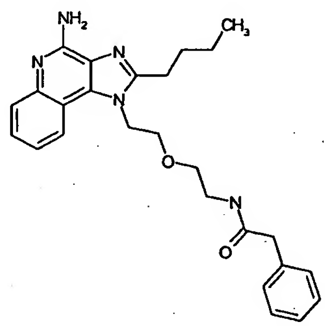
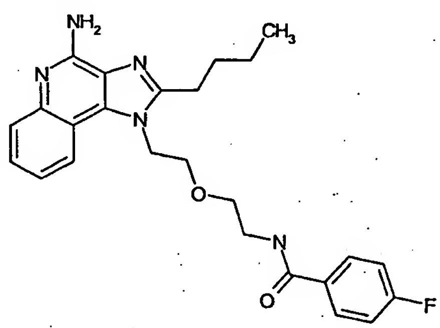
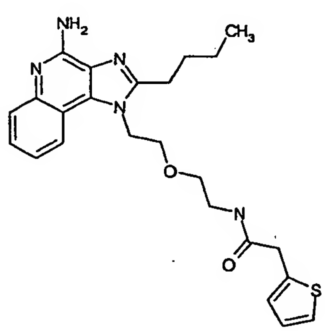
2-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (25 mg, 0.0975 mmol) was placed in a 2 dram (7.4 mL) vial. Sodium hydride (5 mg of a 60% dispersion in mineral oil, 0.117 mmol) and N,N-dimethylformamide (1 mL) were added. The vial was placed on a sonicator for 15 minutes at ambient temperature to allow the alkoxide to form. Methyl bromoacetate (11 µL, 0.117 mmol) was added. The reaction was sonicated at ambient temperature for 1.5 hours. The reaction mixture was analyzed by LC/MS to confirm the formation of the desired product. The reaction mixture was purified by semi-preparative HPLC using Method A Mass Measurement (Da.): Theoretical mass = 328.1535, Measured mass = 328.1534.

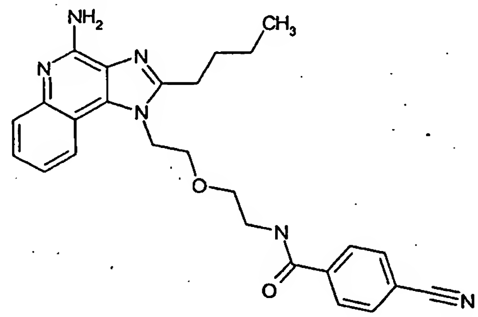
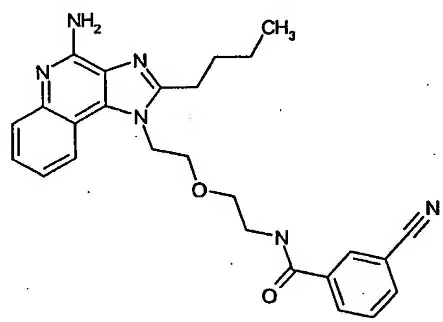
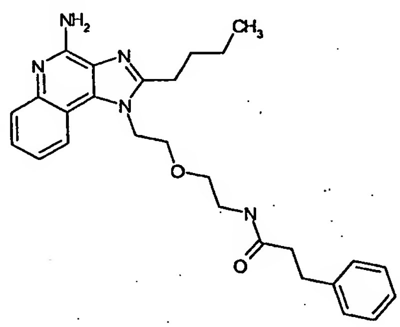
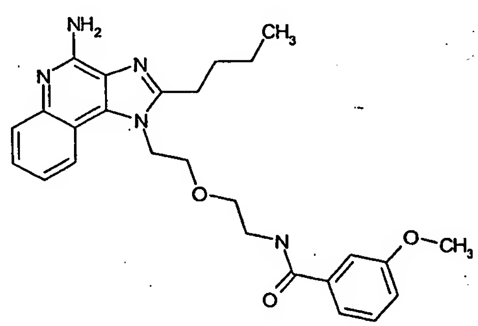
## Examples 15 -34

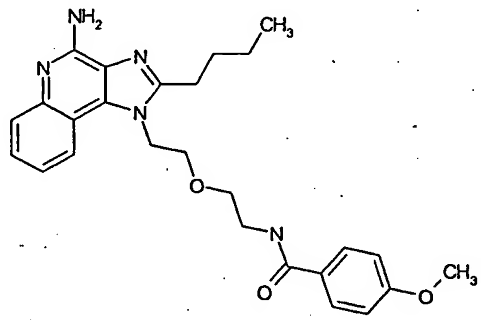
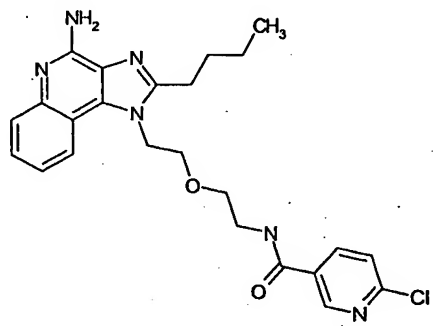
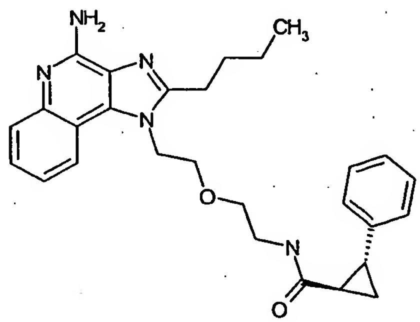
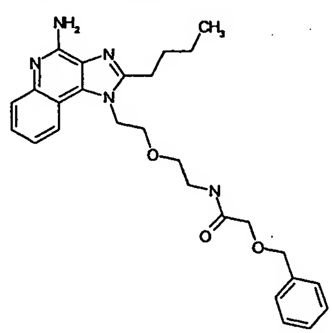
The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme II above using the following general method.

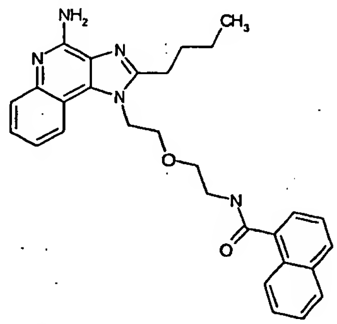
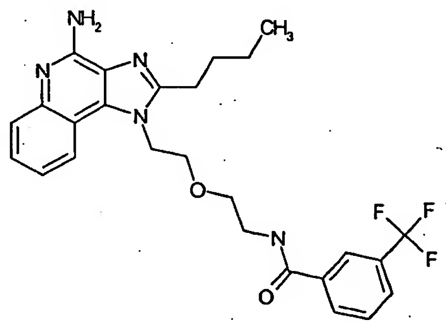
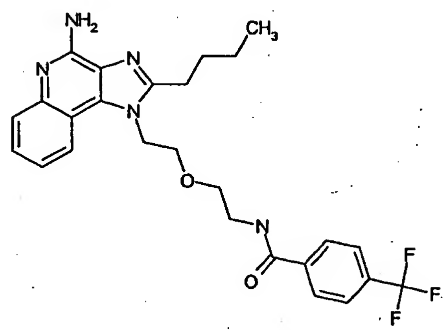
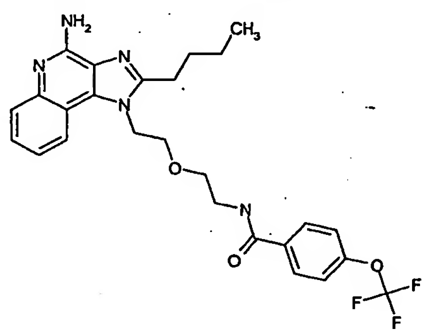
The acid chloride (84µmol) was added to a test tube containing a solution of 1-[2-(2-aminoethoxy)ethyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (25 mg, 77 µmol) in dichloromethane (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum centrifugation. The residue was purified by semi-preparative HPLC using Method B described above. The table below shows the structure of the free base and the observed accurate mass (M + H).

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
| --- | --- | --- |
| 15 |  | 396.2404 |
| 16 |  | 412.2717 |
| 17 |  | 424.2717 |
| 18 |  | 432.2407 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 19 |  | 438.2748 |
| 20 |  | 446.2560 |
| 21 |  | 450.2318 |
| 22 |  | 452.2116 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 23 |  | 457.2369 |
| 24 |  | 457.2333 |
| 25 |  | 460.2693 |
| 26 |  | 462.2529 |

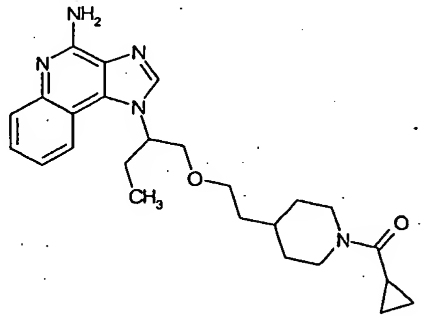
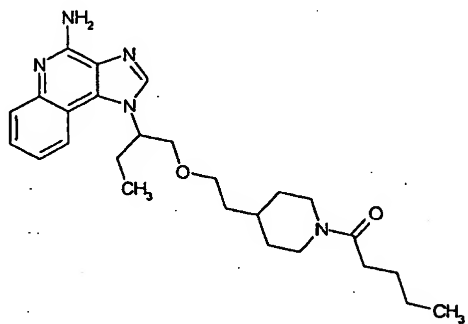
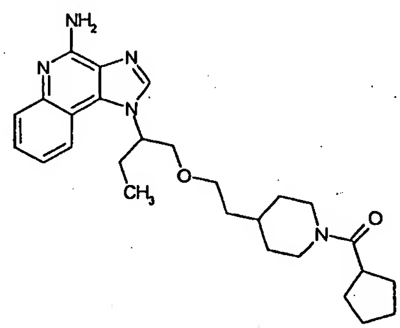
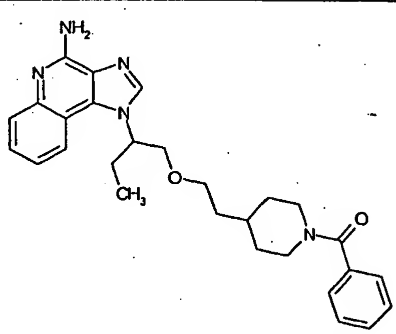
| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 27 |  | 462.2502 |
| 28 |  | 467.1952 |
| 29 |  | 472.2708 |
| 30 |  | 476.2659 |

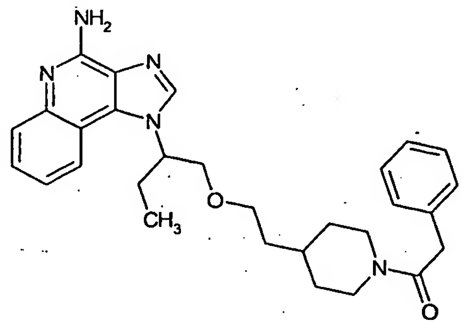
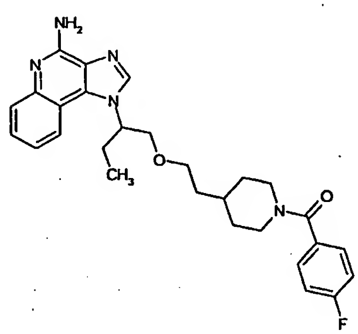
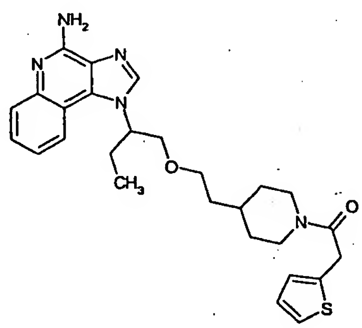
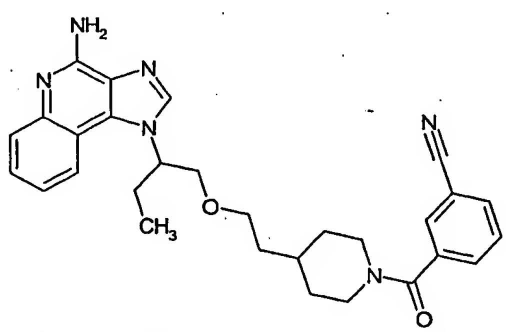
| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 31 |  | 482.2568 |
| 32 |  | 500.2246 |
| 33 |  | 500.2252 |
| 34 |  | 516.2217 |

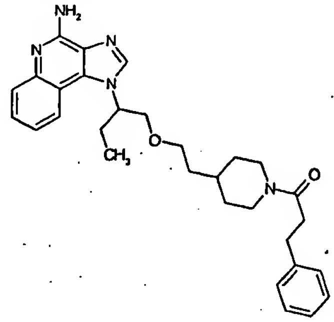
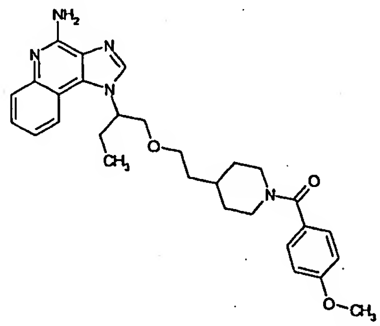
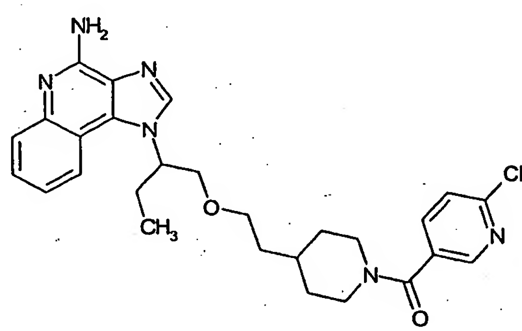
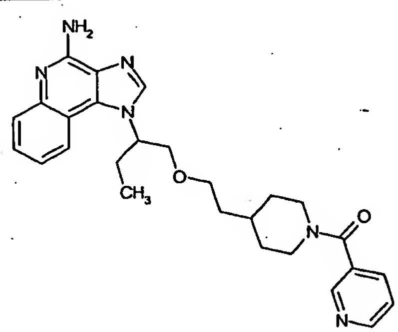
Examples 35 - 51

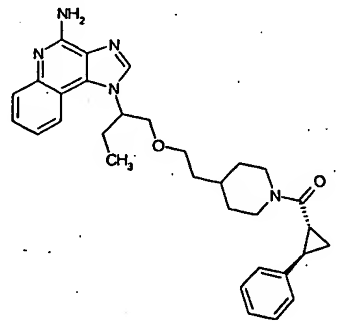
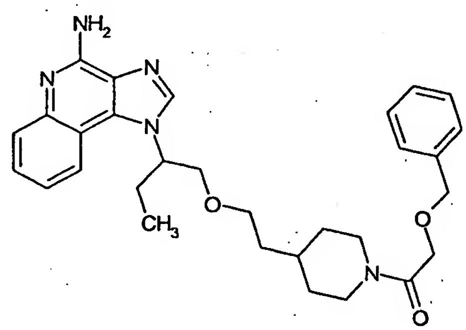
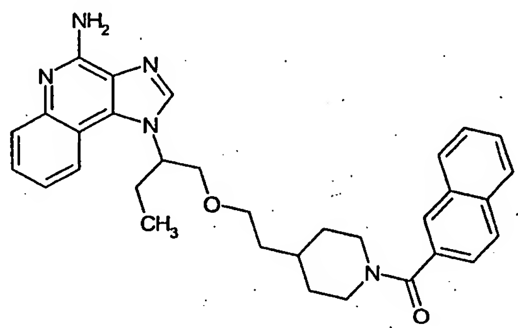
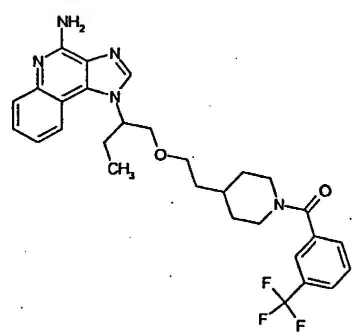
The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme II above using the following general method.

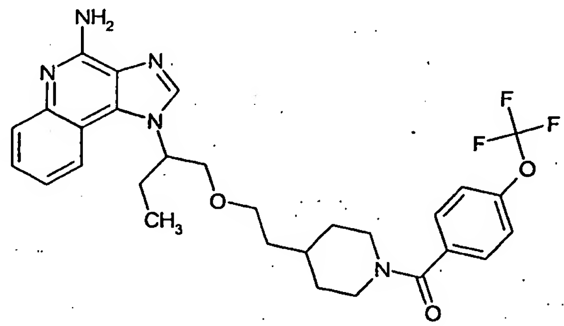
The acid chloride (1.1 eq.) was added to a test tube containing a solution of 1-{1-[(2-piperidin-4-ylethoxy)methyl]propyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (25 mg) in dichloromethane (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum centrifugation. The residue was purified by semi-preparative HPLC using Method B described above. The table below shows the structure of the free base and the observed accurate mass (M + H).

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 35 |  | 436.2683 |
| 36 |  | 452.3014 |
| 37 |  | 464.3045 |
| 38 |  | 472.2717 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 39 |  | 486.2878 |
| 40 |  | 490.2592 |
| 41 |  | 492.2419 |
| 42 |  | 497.2682 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 43 |  | 500.3022 |
| 44 |  | 502.2824 |
| 45 |  | 507.2281 |
| 46 |  | 473.2686 |

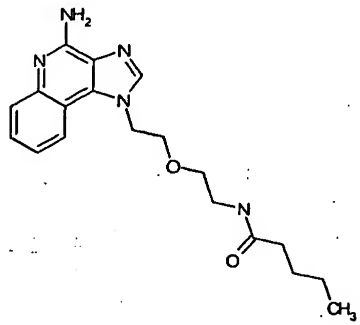
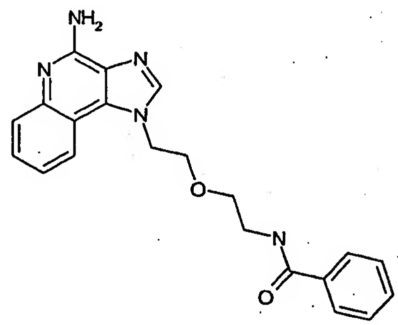
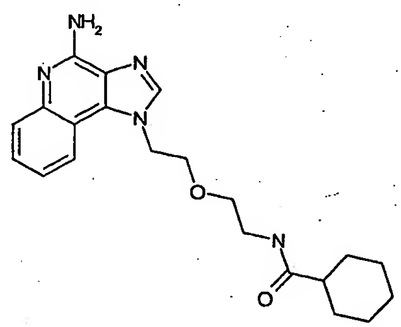
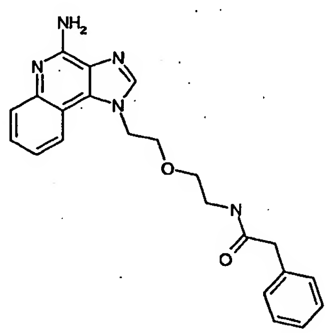
| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 47 |  | 512.3038 |
| 48 |  | 516.2965 |
| 49 |  | 522.2836 |
| 50 |  | 540.2534 |

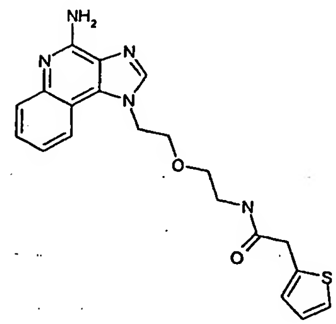
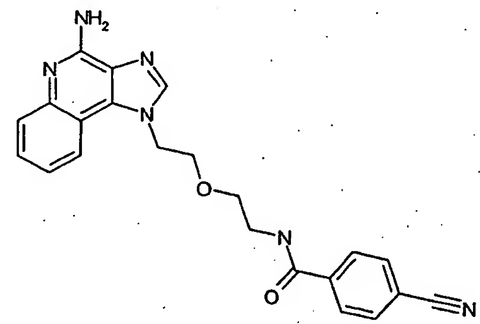
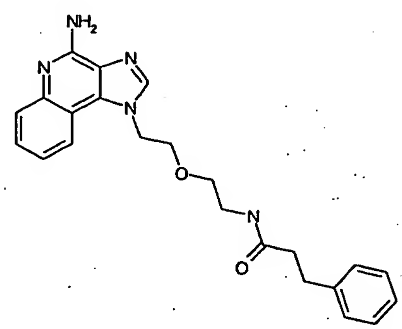
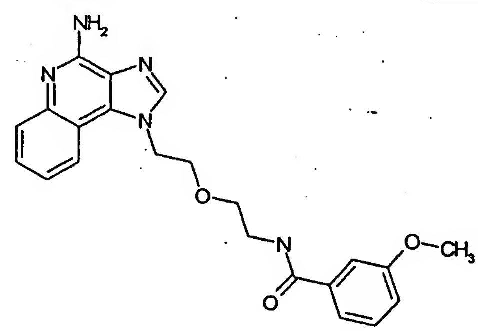
| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 51 |  | 556.2521 |

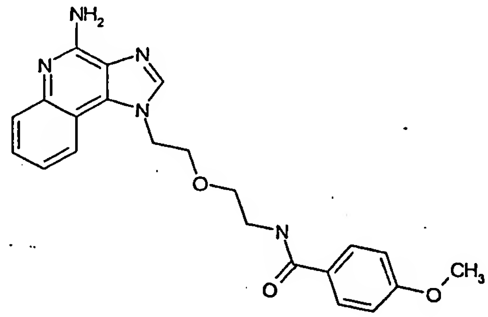
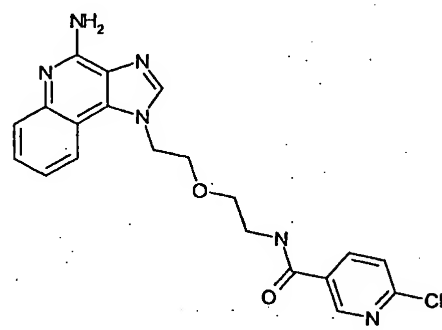
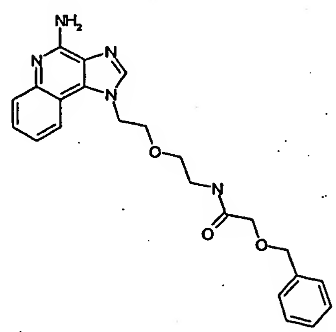
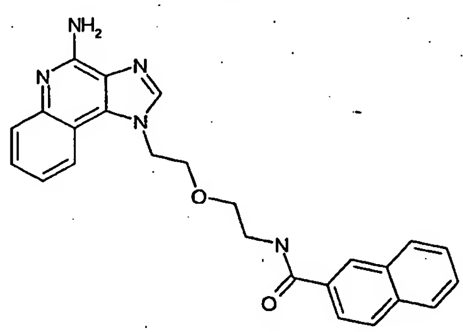
Examples 52 - 66

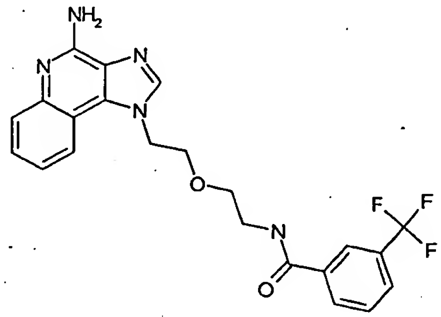
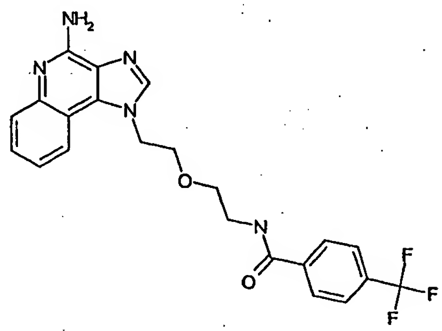
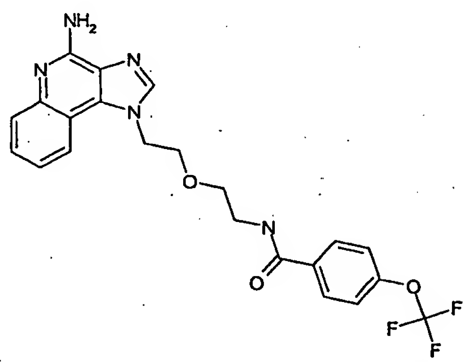
The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme II above using the following general method.

1-[2-(2-Aminoethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (20 mg) and 1-methyl-2-pyrrolidinone (5 mL) were combined in a test tube and sonicated with heating to provide a solution. The acid chloride (1.1 eq.) was added. The test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum centrifugation. The residue was purified by semi-preparative HPLC using Method B described above. The table below shows the structure of the free base and the observed accurate mass (M + H).

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 52 |  | 356.2093 |
| 53 |  | 376.1783 |
| 54 |  | 382.2260 |
| 55 |  | 390.1949 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 56 |  | 396.1503 |
| 57 |  | 401.1707 |
| 58 |  | 404.2105 |
| 59 |  | 406.1855 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 60 |  | 406.1861 |
| 61 |  | 411.1320 |
| 62 |  | 420.2047 |
| 63 |  | 426.1912 |

| Example Number | Structure of Free Base | Accurate Mass (obs.) |
|---|---|---|
| 64 |  | 444.1628 |
| 65 |  | 444.1655 |
| 66 |  | 460.1608 |

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. In "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, **58**, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMCs) are separated from whole blood by density gradient centrifugation using Histopaque®-1077. The PBMCs are washed twice with Hank's Balanced Salts Solution and then are suspended at 3-4 x $10^6$ cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells

Incubation

The solution of test compound is added to the first well containing RPMI complete and serial dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range. The final concentration of PBMC suspension is 1.5–2 X $10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 5-10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) and for tumor necrosis factor (α) by ELISA

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Genzyme, Cambridge, MA; R&D Systems, Minneapolis, MN; or Pharmingen, San Diego, CA. Results are expressed in pg/mL.

The table below lists the lowest concentration found to induce interferon and the lowest concentration found to induce tumor necrosis factor for each compound. A "*" indicates that no induction was seen at any of the tested concentrations; generally the highest concentration tested was 10 or 30 μM.

| Cytokine Induction in Human Cells | | |
|---|---|---|
| Example Number | Lowest Effective Concentration (μM) | |
| | Interferon | Tumor Necrosis Factor |
| 12 | 3.33 | * |
| 13 | 10 | * |
| 14 | 0.37 | * |
| 15 | 0.1 | 1 |
| 16 | 0.1 | 1 |
| 17 | 1 | 1 |
| 18 | 1 | 10 |
| 19 | 1 | 10 |
| 20 | 0.1 | 10 |
| 21 | 1 | 10 |
| 22 | 0.1 | 10 |
| 23 | 1 | 10 |
| 24 | 1 | 10 |
| 25 | 1 | 10 |
| 26 | 1 | 10 |

| Cytokine Induction in Human Cells | | |
|---|---|---|
| Example Number | Lowest Effective Concentration (μM) | |
| | Interferon | Tumor Necrosis Factor |
| 27 | 1 | 10 |
| 28 | 1 | 10 |
| 29 | 1 | 10 |
| 30 | 1 | 10 |
| 31 | * | 10 |
| 32 | * | 10 |
| 33 | * | 10 |
| 34 | * | 10 |
| 35 | 0.1 | 1 |
| 36 | 1 | 1 |
| 37 | 1 | 1 |
| 38 | 1 | 10 |
| 39 | 1 | 10 |
| 40 | 1 | 1 |
| 41 | 0.1 | 1 |
| 42 | 1 | 1 |
| 43 | 1 | 10 |
| 44 | 1 | 1 |
| 45 | 0.1 | 1 |
| 46 | 0.1 | 1 |
| 47 | 1 | * |
| 48 | 0.1 | 10 |
| 49 | 1 | 10 |
| 50 | 1 | 1 |
| 51 | 10 | 10 |
| 52 | 10 | 10 |
| 53 | 10 | 10 |
| 54 | 10 | 10 |

| Cytokine Induction in Human Cells | | |
|---|---|---|
| Example Number | Lowest Effective Concentration (μM) | |
| | Interferon | Tumor Necrosis Factor |
| 55 | 1 | 10 |
| 56 | 1 | 10 |
| 57 | 10 | * |
| 58 | 10 | 10 |
| 59 | 10 | 10 |
| 60 | 10 | 10 |
| 61 | 10 | 10 |
| 62 | 1 | 10 |
| 63 | * | 10 |
| 64 | 10 | * |
| 65 | * | * |
| 66 | * | * |